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Child's Nervous System

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Child's Nervous System

CNS

Official Journal
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The official journal of the International Society for Pediatric Neurosurgery (ISPN) was founded in 1972 as *Child's Brain.* As of 1 January 1985, the Society changed publishers. The new official journal, *Child's Nervous System,* – with the same editor – has now been expanded to encompass all aspects of the pediatric neurosciences: development and growth; trauma; degenerative disorders; hereditary diseases; neurophysiology, neurology, and neurosurgery. The journal is designed, therefore, to be read by physicians active in the care of children with disorders of the brain and spinal cord. Original manuscripts are given priority for publication, although individual case reports will be accepted. A given issue may contain a special review article by an authority in the field, assigned and submitted critiques of current and previously published papers, book reviews, and letters to the editor. Letters to the editor concerning the socio-economic conditions of pediatric neurosurgery in individual countries are also welcome.

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Editor's note

Child's Nervous System GNS

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Child's Nerv Syst (1992) 8:1

The International Society for the Pediatric Skull Base was officially incorporated in Munich, Germany, on 23 November 1991.

The subjects of the first scientific meeting will be: (1) General Concepts; (2) Mid-face, Orbit and Anterior Fossa; (3) Parasellar Area and Rhinopharynx; (4) Petrous Structures and Middle Fossa; (5) Clivus, Posterior Fossa and Cranio-vertebral Junction.

You are invited to submit an abstract for presentation to the First Scientific Congress of the International Society for the Pediatric Skull Base, to be held in Hannover, 12–14 June 1992. Send your abstract to Dr. Shizuo Oi, Department of Neurosurgery, Kobe University Medical School, Kusunoki-cho 7, Chome Chuo-Ku, Kobe, Japan.

Charter Membership will be granted to qualified applicants who register for the Hannover Meeting. For details regarding Membership, contact the Secretary, Dr. Thomas Wustrow, Klinik und Poliklinik für HNO, Marchioninistrasse 15, W-8000 München 70, Federal Republic of Germany.

The formal announcement regarding the First Scientific Congress and the Abstract forms are now being mailed.

Letter to the editor

Child's Nervous System GNS

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Child's Nerv Syst (1992) 8:2–3

Corpus callosotomy for intractable seizures in the pediatric age group: influence on frontal syndrome

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Sir:

We have performed 8 anterior callosotomies in patients with intractable epilepsy, especially those with generalized atonic or tonic seizures, during the past 2 years. The fits came from generalized bilateral spikes or from frontal spikes. In all patients, we observed a significant decrease in the number of epileptic crises, and a very considerable improvement in such neuropsychological behavior as frontal syndrome, described with epilepsy in the literature [5] and related in our experience to changes of cerebral flow observed at single-photon emission computerized tomography (SPECT).

We thought that a mention of 2 children in our group would be of value. The first, a 13-year-old boy with a history of brain injury at birth, developed intractable epilepsy at the age of 6 months and then mental retardation. Despite treatment with phenobarbital, sodium valproate, carbamazepine, and clonazepan, he had experienced 1–2 atonic seizures per day since the age of 3 years. Behavioral changes, reported by the parents since the age of 10 years, were characterized by aggressiveness, distraction, echolalia, echopraxia, and alexithymia. He had grasp and snout reflexes, was unable to repeat a series of five names of animals, fruits, or vegetables, and was unable to perform movements simultaneously with both hands. These symptoms were included in a frontal syndrome demonstrated by EEG recording of frontal spikes, a CT scan showing frontal atrophy, and SPECT showing low frontal lobe blood flow. His IQ, measured by the WAIS test, was 75. The Wada test revealed no language center on the right.

Offprint requests to: M. Giroud

After anterior callosotomy performed from the right, we observed no disconnection syndrome, but an 80% decrease in atonic seizures within 2 years. We also observed a marked improvement in behavior, with progressive disappearance of the frontal syndrome within 3 months of corpus callosum surgery. This latter was characterized by improvement in memory, language, and school performance. The frontal spikes persisted but the frontal blood flow had become normalized in SPECT 3 months after surgery, without changes in pharmacological treatment.

In the second case, a 15-year-old girl developed cryptogenic frontal epilepsy at the age of 1 year. From the age of 4 years she had at least one tonic seizure per week and one generalized tonic-clonic seizure per day, notwithstanding treatment with phenobarbital, sodium valproate, and carbamazepine. CT and magnetic resonance findings were normal. Frontal spikes were observed in many EEG recordings, and 3 clinical frontal seizures were registered. A frontal syndrome was clinically evident at least 1 year before surgery, characterized by aggressiveness, bradypsychia, alexithymia, and grasping reflex. The child was unable to give a series of five names of fruits or animals, nor to perform opposite movements with her two hands. Graphic tests showed a "closing-in" phenomenom. Her IQ score was 85. SPECT revealed a decrease in frontal blood flow.

After surgery under the same pharmacological treatment, the tonic seizures disappeared during the 1st year, with only one tonic-clonic seizure per week, and the frontal syndrome disappeared within 3 months. Repeat SPECT gave normal results. No disconnection syndrome was observed, and memory was improved.

We report on these two cases in order to stress the place of the frontal syndrome in the genesis of behavioral changes observed in patients with intractable seizures. The frontal syndrome diagnosis relies on clinical, EEG, and SPECT features.

Secondly, frontal syndrome disappears after anterior callosotomy together with a reduction of generalized tonic-clonic or tonic or atonic seizures, with any change in pharmacological treatment. This clinical improvement is confirmed by SPECT imaging.

We have not noticed the psychological deterioration reported by Sass et al. [4] and agree with Geoffroy et al. [1], Papo et al. [3], and the results of 58 instances of corpus callosotomy for intractable seizures in the pediatric age group less than 16 years old, reviewed by Nordgren et al. [2], in concluding that partial anterior callosotomy

has no negative behavioral consequences. Morever, this operation can improve such intellectual functions as memory and global performance, resulting in the disappearance of a preoperative frontal syndrome induced by aggravation of generalized seizures, as shown in our two cases.

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Essay

Child's Nervous System CNS

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The education and identification of a pediatric neurosurgeon *

Anthony J. Raimondi

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Abstract. Pediatric neurosurgery very likely became an entity because of the admission of children with CNS diseases to children's hospitals and the development of subspecialization. This latter, in pediatric neurosurgery, has been more a result of events, such as the individual's working propinquity to other pediatric specialists and his being comfortable with children and their parents, than of methodical adherence to a philosophical precept. A fellowship in pediatric neurosurgery, in my opinion, has negative value, in that it would create a working/learning situation in which the fellow would take essential educational and responsibility experiences from the resident and would be delegated patient-care and teaching accountabilities he is not ready to assume. Two, more appropriate, alternatives could be either an additional year as a resident, or a proper staff appointment, depending upon the candidate and the institution. The pediatric neurosurgeon, like other subspecialists in our discipline, may be identified on the basis of what he does, how well he does it, and which societies recognize him as member. Since subspecialization as we see it today is inevitable and represents progress, a certificate (in the subspecialty of pediatric neurosurgery) awarded by the American Board of Neurosurgery would have positive implications, as would, for example, a Continuing Education Award, given by the AANS, the CNS, or the American Society for Pediatric Neurosurgery. Such certificates or awards could serve differing purposes or provide differing recognition as the life of our subspecialty unfolds.

Key words: Pediatric neurosurgery – Fellowship – Board certification – Subspecialization

If we wish to understand completely and to feel fully the impact teaching (an apparently noble, generous, if not altruistic activity) may have on groups of men who feel comfortable with their present state of knowledge, we should for a moment pause to remember the adverse responses to Socrates, Jesus, or Scopes [1] of the "Monkey Trail", only to see in perspective how well received men like Aristotle, Morgagni, and Oliver Wendell Holmes were. It has not been possible to understand why some were pilloried and others praised, although, clearly, in conveying their messages some (the latter) sought only to offer alternate ways of thinking, while others (the former) suggested nothing less than changes in the nature of mankind.

Trends, resulting from research and education, in professional specialization in the various disciplines of medicine have in some instances been both well received and encouraged, but in others have been discouraged if not obstructed.

Pediatric neurosurgery is not having an easy time gaining acceptance or recognition from organized neurosurgery, neither in America nor in the rest of the world. Why is this? Are we, the pediatric neurosurgeons telling general neurosurgeons that we wish to be left to ourselves? That we wish to control not only the scientific and technical aspects of patient care, but also the educational and ethical aspects of pediatric neurosurgery? Are we conveying the message that we do not wish to function within the confines of and be governed by our parent specialty? The answer to these questions, I fear, is "yes".

This estrangement of pediatric neurosurgery may stem from particular experiences and tendencies. It became an entity within children's hospitals, very probably because of the combination of (1) an ongoing association with clinicians in other pediatric specialties and (2) the structural organization alongside orthopedics, hematology, radiology, etc., within the pediatric hospital. The spread from the neurosurgical care of a child in a pediatric hospital to the contemplation of a professional activity conducted only by those who limit themselves entirely to the care of children may have been more a consequence of

* Presented at the XI Annual Meeting of the American Society for Pediatric Neurosurgery, Peter Island, B.V.I., February 1988

[1] Raymond Ginger, Six Days or Forever? Tennessee vs. John Thomas Scopes (1958)

association with the other clinicians in the children's hospitals than of methodical adherence to a philosophical precept.

Unfortunately, the innuendo that one who refers to himself as a "pediatric" neurosurgeon is "ennobled by the title to remove tumors from a child better than an individual who does not have that title" was there, and its existence has been a problem. It has garbled communication, so that the true differences – an innate ability to relate to a sick child, having acquired skills which permit interrelationships with the anxious and demanding parents, being comfortable working in a pediatric setting, and having a willingness to work in fields which do not interest other neurosurgeons – have neither been seen nor accepted.

Very similarly to what occurred among other neurosurgeons who subspecialized, conferences, courses, seminars, and meetings were held. The same dynamics were active with regard to journals. In sum, the logistics made separate meetings, within what is the general body of neurosurgery, necessary. Thus, the processes culminating in a pediatric neurosurgeon and pediatric neurosurgery were natural and evolutionary, not planned.

Education

Pediatric neurosurgery is a science, an art, an ongoing life's work. One cannot educate a pediatric neurosurgeon for the future in either a postgraduate course or a 6- or 12-month fellowship. The turnover in available knowledge and in the state of the art is rapid, even though there is the to-and-fro phenomenon which brings us back repeatedly in the direction from whence we came. It is, however, possible to recognize certain areas of professional competence to which someone who identified at an early stage his/her field of interest as pediatric neurosurgery must be exposed: neurosurgery, neurodiagnostics, and pediatrics.

I am of the opinion that one cannot be an excellent pediatric neurosurgeon unless he is first an excellent general neurosurgeon, and then only if his background is broad, including extensive experience in adult neurosurgery with trauma, neoplasms, and vascular pathology. The risk is that one may become identified as a shunt surgeon, who also closes meningomyeloceles (pediatric neurosurgeons appreciate fully the fact that shunt surgery is difficult, extremely difficult, and that the procedure should not be relegated to the lower echelons of technical competence). Thus, it is essential that there be a place in every large service for a surgeon who "specializes" in shunts and another for the individual who is most comfortable with the dysraphic state. Nevertheless, we must recognize the fact that two operations do not make a specialty. Therefore, a complete residency in adult neurosurgery, with a 6-month rotation through an active pediatric neurosurgical service, is essential as a point of departure.

A matter that has attracted much attention is that of a fellowship in pediatric neurosurgery: a fellowship in the true sense of the word, not a residency, not a proper staff appointment. There is nothing positive, but there is much that is negative, in this. A fellow takes from the resident necessary experiences; he is delegated, by the staff, responsibilities he is not ready to assume. He is in the awkward position of being both student and teacher, of being called upon to make the judgments and carry out the procedures of a subspecialist while his knowledge and technique are yet to be acquired. A fellowship, be it for 6 or 12 months, is an inadequate preparation for the title *pediatric neurosurgeon*. Candidates to become pediatric neurosurgeons should join the staff and then be brought along by their teachers and peers until they fit snugly into the specialty. If certifying bodies and Boards throughout the world do not wish to recognize pediatric neurosurgery as a subspecialty, they should not go half-way by authorizing and structuring fellowships.

We must avoid running the risk of taking on "fellows" *to help out with the workload*, people who will then go out to function independently, generally in settings we would consider unacceptable for the practice of our subspecialty. This, of course, does not apply to accepting, as observers, responsible and dedicated individuals from Third World countries who wish to see what we do, how we organize and conduct our services, what our results are, and how we analyze them. They should be welcome to make rounds, observe surgery, participate in conferences, and review records.

Identification

The matter of "identification of a pediatric neurosurgeon" is presently of considerable importance to many. Should a certificate of special competence be the seal of approval? Or, rather, should pediatric neurosurgeons be recognized by virtue of what they do, how well they do it, and whether they keep abreast of the progress in the subspecialty and the society to which they belong? The members of a responsible society for pediatric neurosurgery, for example, the American Society for Pediatric Neurosurgery, by virtue of their preparation and vocation, *identify* one as a pediatric neurosurgeon by accepting him within their ranks. The acceptance is professional, not social, rendering public the approval of the individual by his peers.

Should there be a Board of Pediatric Neurosurgery? A Board, if established, would consist of a group of people representative of pediatric neurosurgeons who form both analytic and synthetic functions. These functions are limited in scope. They consist of reviewing educational credentials, establishing criteria for evaluating minimum acceptable standards for admission to and satisfactory passing of the examination, selecting questions, and administering the examination.

The inspection of universities, hospitals, and clinical services, the evaluation of faculty, facilities, clinical load, support personnel, and specialty units, the interrelationships with approved neurosurgical training programs and affiliated specialties, such as pediatrics, neurology, and diagnostic neuroradiology, and periodic site visits to

evaluate compliance, in the United States are within the competence of the Residency Review Committee[2].

Board certification in pediatric neurosurgery would have a positive value only: attesting to compliance by an individual with the established requirements. It would have no negative value: no mechanism for prohibiting fully certified general neurosurgeons from operating on children of all ages for any surgical disease process of the central nervous system. If the latter were attempted, it would, I suspect, be resisted by the American Board of Neurological Surgery (ABNS).

I also think that the establishment of a separate board for the purpose of issuing a special certificate or diploma would, in time, separate pediatric neurosurgery from the parent specialty, resulting in relative isolation from neurosurgery and incorporation into pediatrics. The basis for this conclusion may be found in those children's hospitals that are remote to the parent university neurosurgical service: the centrifugal force resulting from the explosive motivation toward "independence" may serve more to fragment knowledge and techniques than to guarantee profound scientific concepts and skills. Most important, such a Board could not prevent any other group of practitioners from doing the same. For example, if today a group of pediatric neurosurgeons decided to identify certain hospitals where training could be gotten, establish training criteria, examine and "certify" candidates, any other group (stereotaxic, interventional, neuro-oncologic, radiologic) could either do the same or challenge the criteria. The ABNS would only need to emphasize that *its* certification attests to competence in neurosurgery in all aspects (as in fact it does).

At present, we must conclude that the ABNS in general, and American medicine in particular, recognize pediatric neurosurgery *de facto* and that they do not want to do this *de jure*. There is reluctance in organized neurosurgery to separate off a chronological category (pediatrics), as there is to separate off an anatomical category (vascular), an etiological category (trauma), or a technical category (stereotaxic or microscopic). This is true of all the national neurosurgery societies that I know, whether American, Japanese and Asian, European, or Latin American. The public and legal profession recognize the subspecialty and ask for no jurisdictional body to give it a stamp of approval. The complete dominance of craniofacial anomalies by plastic surgeons, albeit with the symbolic presence of a neurosurgeon to reflect the scalp flap, is a fact worldwide.

What, if we were organized *de jure* into the specialty of pediatric neurosurgery, would our position be *vis-a-vis* the stereotaxic specialty for biopsies and brachytherapy, the etiologic specialties of traumatology and oncology, the pathoanatomic specialties of vascular and vertebral column, if they were to claim that their knowledge and instrumentation are such that they alone should perform stereotaxic biopsies or brachytherapy and manage head injuries or trauma or vascular pathology or tumors in all age categories? With what reasoning could we refuse to encourage their development?

So that these examples may not appear purely argumentative, I call attention to stereotaxic EEG recording as a guide to destroying epileptogenic foci, brachytherapy for midline tumors, radiosurgery for gliomas and AVMs, all developing, highly specialized areas within neurosurgery. I would place particular emphasis on the developing, interdisciplinary specialty of skull base surgery! Where would our Chiari II children go for reconstruction of the skull base? To a "general" pediatric neurosurgery service, or to a skull-base service?

Board certification is an anachronism for subspecialties such as ours. It was established originally as a meter against which the "training" and knowledge of a specialist could be measured, to obtain a certificate in times when communications were slow, journals were few and multidisciplinary, and scientific meetings and specialty review courses nonexistent, when conferences among physicians interested in a special subject – a specialty – were in the true sense of the word clubs. It was necessary when the public was wont to regard all doctors as competent in all fields, when doctors could do what they chose (as they saw fit) at that moment: when, in fact, "peer review" did not exist.

Specialization and board certification, along disease-oriented or organ system lines, were positive steps away from this helter-skelter system, steps which resulted in significant advances in knowledge, technology, and patient care at a time when most physicians died with the same knowledge they had acquired in medical school, enriched only by their own personal observations and experiences.

Some countries, highly industrialized or Third World, may still have much to gain by instituting a board system for major specialities, but I do not think a board system for subspecialized areas is a positive move. The boards themselves have within their structure and function the means by which professional competence, specific professional competence, may be evaluated and registered. It is unfortunate that our Board have not yet encouraged and facilitated subspecialization *within* neurosurgery as academic disciplines.

I said that for a subspecialty such as ours the board system is an anachronism. I regard this as the case for the two already alluded to reasons: "peer review" and the "free spirits." With regard to the "free spirits," there are now great numbers of socially motivated physicians specializing in neurosurgery and other fields which do or may interact with pediatric neurosurgery, that is, *with the treatment of disease of the child's nervous system which we, today, consider to be pediatric neurosurgical diseases*. The ever-budding "free spirits" are those physicians, young or old, who see things differently. They are "free" to apply alien data or concepts to the orthodox world of a structured and monitored specialty. By their very nature, the "free spirits" readily join other groups, generally giving both energy and substance, seldom stabilizing or hardening positions.

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[2] In the United States this is composed of representatives of the Association of American Medical Colleges (AAMC), the American Medical Association (AMA), and the Association of American Medical Specialties (AAMS)

As these physicians, inspired to treat these diseases, elaborate their concepts, develop their techniques, accumulate their experiences, and refine their methodology to the point where the principles may be transferred to others, for application to the management of sick children everywhere, we want them with us. They are developing interventional neuroradiology, plastic surgery, skull base surgery and radiosurgery. They cannot be limited by age categories.

With regard to "peer review," pediatric neurosurgery has an internationally accepted language, English; we have organized ourselves into societies; we conduct numerous postgraduate courses; we have journals, yearbooks, and series. Complete blocks of time are given to us in the programs of major neurosurgical congresses.

Of particular interest in the evolution of the identification of pediatric neurosurgery were the Seventh Annual Meeting of the Congress of Neurological Surgeons and the fifth volume of *Clinical Neurosurgery*. With only two exceptions (presentations by the Honored Guest, Francis C. Grant, on skull base meningiomas and cordotomy), the papers (all invited by the program committee) were "devoted to the problems of neurological surgery in childhood."[3]

We are recognized as pediatric neurosurgeons, and we among ourselves know well who does what and how. This is identification by one's environment. In fact, adult neurosurgery, pediatrics, our communities all accept us. In the U.S.A., the American Society for Pediatric Neurosurgery has, wisely I think, *after* its organizational meeting, been careful to select for membership just those people who, by profession and vocation, are pediatric neurosurgeons. The identification of a pediatric neurosurgeon is clear and immediate.

Conclusions

Pediatric neurosurgery is learned best as a neurosurgery resident, and subsequently as a pediatric neurosurgery staff member. The residency time should not exceed 6 months, unless an individual chooses to prolong his residency training. Extra time should not be at the expense of adult neurosurgery experience. I think that a fellowship is an undesirable alternative in that it necessarily takes clinical experiences from the rotating residents, and it results in staff personnel delegating surgical supervision and educational responsibilities to individuals who, in fact, are there to learn. Consequently, it is particularly undesirable in that it may serve as a mechanism for adding fully trained neurosurgeons to the staff, at a non-descript level, to discharge specialized responsibilities that they are not yet prepared to manage. It would soon result in producing ever-increasing numbers of "qualified" pediatric neurosurgeons. Later in their professional lives these "specialists" in pediatric neurosurgery may not have enough to keep themselves busy, so they could work in general neurosurgical groups, doing pediatric *and* general neurosurgery. When they are not available, their pediatric cases would be managed by general neurosurgeons. What will have been accomplished?

A Board of Pediatric Neurosurgery is neither necessary nor desirable. Such a Board would, in my opinion, lead to restructuring of our subspecialty, creating rigid predetermined criteria for compliance that would be more confining than a developing specialty such as ours should permit itself to tolerate. It would entail establishing, organizing, and duplicating all the functions already in existence in the ABNS.

Subspecialization is progress and it is inevitable. A certificate in the subspecialty of pediatric neurosurgery would have positive professional, academic, and practice implications. These could easily be adapted to serve different purposes and provide differing recognition as the life of our subspecialty unfolds, reacting to the situations and disease entities it encounters. It could be awarded by the ABNS as it is presently constituted, and it could be renewed periodically in accordance with criteria that result from continued practice and educational experiences. Similarly, a Continuing Education Award, issued by the AANS, the Congress, or the ASPN could serve the same purpose, provide the same recognition. Such a certificate or award would keep the subspecialty of pediatric neurosurgery in general neurosurgery.

Our specialty, general neurosurgery, by and large has not prepared organizationally for subspecialization, and it has remained too traditional. We do not, because of organizational conservatism (not inertia!), lead. We are so busy reacting that we cannot reflect; we are so highly structured that we cannot respond adequately to changing technology and new concepts. Hence, the subspecialists seem to be more comfortable in other specialties, or alone. Could this not also occur in the subspecialty of pediatric neurosurgery? It would be a pity!

In sum, the pediatric neurosurgeon should be an exceptionally well-trained adult neurosurgeon who goes on to dedicate his professional activities primarily or exclusively to pediatric neurosurgery, working in an appropriate setting with appropriate peers. His identification should be based upon what he does, how he does it, and which professional societies recognize him. This, of course will vary from one country to another. In the United States, the ASPN could include in its membership *all* those who are primarily or exclusively engaged in this subspecialty. Identification as a pediatric neurosurgeon in the U.S. could be the responsibility of this Society, in that it would express recognition by peers, fellow members of the ASPN.

As other geographic areas or countries educate enough pediatric neurosurgeons to form societies limited to those practicing primarily or exclusively pediatric neurosurgery, the same could apply. The pediatric neurosurgeon, as pediatric neurosurgery, cannot live in the world of neurosurgery and outside that of pediatrics, or vice versa; he cannot live alone, independent. He must be a neurosurgeon "devoted to the problems of neurological surgery in childhood."

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[3] Robert G. Fisher, Editor-in-Chief, *Clinical Neurosurgery*, vol V, 1957, Waverly Press

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Morphological substrates of infantile spasms: studies based on surgically resected cerebral tissue

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Abstract. Extensive surgical resections of neocortical cerebral tissue (including hemispherectomies) from 13 infants and children with infantile spasms showed that 12 of 13 specimens contained either malformative and dysplastic lesions of the cortex and white matter (sometimes with associated hamartomatous proliferation of globular cells), or destructive lesions possibly acquired as a result of anoxic-ischemic injury, or a combination of the two. In brain tissue from 4 patients, coarse neuronal cytoplasmic fibrils resembling neurofibrillary tangles were seen in areas of dysplastic brain on silver-stained (Bielschowsky technique) sections. Immunohistochemical (immunoperoxidase) study of cortical lesions containing globular cells employing primary antibodies to glial fibrillary acidic protein and synaptophysin as markers of astrocytic and neuronal differentiation, respectively, revealed that many cells showed astrocytic and/or neuronal features, suggesting the local proliferation of primitve or multipotential neuroectodermal cells as one substrate for this seizure disorder. Morphological abnormalities of a severe degree and wide extent in the resected tissue (e.g., in one patient with hemimegalencephaly) often showed features to suggest that they may represent variants of tuberous sclerosis. These most likely result from abnormal movement and/or local proliferation of neuroectodermal precursors that have migrated from the germinal matrix to the cortical mantle. Cellular, molecular and neurophysiological study of these abnormalities is likely to yield information about basic molecular mechanisms of brain malformation and injury important in the pathogenesis of infantile spasms and other forms of focal or generalized epilepsy.

Key words: Infantile spasms – Brain, malformations – Dysplasia, cortical – Hemispherectomy – Epilepsy – Immunocytochemistry – Hamartomas, CNS

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From a neuropathological viewpoint the spectrum of morphological correlates of infantile spasms is extremely heterogeneous [27]. Studies which have examined structural lesions in the brain that result in infantile spasms have virtually all been carried out on postmortem material, thus complicating precise assessment as to the significance or etiology of a given lesion, i.e., is it a cause of infantile spasms or the result of a prolonged seizure disorder [3, 27, 34, 44]?

We report the results of a detailed morphological (including preliminary ultrastructural and immunohistochemical) study of 13 cortical resection specimens derived from patients in whom infantile spasms had been a major neurological problem. In all individuals, multilobar cortical resection or hemispherectomy led to significant improvement in seizure control. We present novel observations on neuronal cytoskeletal abnormalities that are observed in dysplastic lesions associated with infantile spasms. Immunohistochemical study of these dysplastic lesions suggests that at least one neuropathological substrate of infantile spasms is the hamartomatous proliferation of multipotential neuroectodermal cells within cerebral cortex and white matter. Portions of the work have previously been presented in abstract and preliminary publication form [60–62].

Materials and methods

The tissue studies were carried out on 13 patients, with an age range of 3 months to 5 years 1 month at the time of surgery. Clinical details and results of imaging studies on these patients have been or will be presented in other publications and will not be reviewed here. Findings of positron emission tomographic (PET) scans on 4 of the individuals from whom tissue was examined have previously been reported by Chugani et al. [5]. The first 4 patients in their series (and Patient Summary) are represented as patients 4, 5, 7 and 9, respectively, in the present publication. Five patients were male and 8 were female. Seven patients had a total cerebral hemispherectomy (3 on the left side, 4 on the right) while the remaining 6 had multilobar resections, usually involving the parietal, occipital and temporal lobes. Tissue processing was similar to that for cortical specimens removed in the course of surgical treatment of temporal lobe

epilepsy. In this laboratory, all specimens are fixed for at least 3–6 days in 10% neutral buffered formalin, and are then sliced coronally. Blocks are taken as per a predetermined blocking diagram to ensure relatively uniform sampling of topographic regions of the resection specimens from patient to patient. Given the extensive neuropathological change in many of the cortical specimens, this uniformity of sampling is not always possible. Embedding is in paraffin, although in many instances tissues are also snap-frozen for immunohistochemical study and placed in appropriate fixatives for electron microscopy.

In specimens from patients with malformative lesions, immunohistochemical study of paraffin or frozen sections was carried out using standard avidin-biotin immunoperoxidase histochemical techniques and employing primary antibodies to synaptophysin or glial fibrillary acidic protein (GFAP) [13, 17, 32]. In some patient tissues, sequential dichromatic immunohistochemistry was carried out using a monoclonal antibody to the neuronal marker synaptophysin (Boehringer, Mannheim) at a dilution of 1:5, followed by overnight incubation and staining with polyclonal antibody to the specific astrocytic marker GFAP (Cambridge Research Laboratory/Ortho Diagnostic) at a dilution of 1:500. Cobaltous acetate toning of the diaminobenzidine (DAB) reaction product for the first antibody allowed detection of differential localization of the two antigens. Toning causes the DAB reaction product to turn a blue-black color, allowing for differentiation between this and the brown reaction product produced after a standard DAB reaction. TRIS-buffered saline was used as the diluent for the peroxidase-labeling step, and stop rinses were carried out using phosphate-buffered saline (PBS). Controls included runs in which each of the primary antibodies was used alone. Positive controls were staining procedures carried out on tissue specimens known to show strong and appropriate focal positivity after staining with each of the primary antibodies.

Another method used to establish antigen co-localization was to treat sections with anti-synaptophysin antibody first, using DAB as the chromogen, followed by overnight rinses in PBS with 0.01% Triton X-100. Sections were then treated with normal goat serum (3% in PBS) and rabbit anti-GFAP at a dilution of 1:500 for 1 h. Secondary biotinylated goat anti-rabbit antibody was applied at a dilution of 1:10 (30 min). Equivalent volumes of avidin and biotinylated glucose oxidase (Vector Laboratories: AB-GO kit) in PBS were then applied to tissue sections for 30 min. This resulted in a blue (formazan) reaction product upon treatment with nitro-blue tetrazolium salt (for GFAP) that could be easily distinguished from loci in which synaptophysin was present. Both reaction products were visualized together in sections that were not counterstained.

Results

Table 1 summarizes the neuropathological findings in the 13 specimens examined. Only 1 patient had minimally abnormal-appearing cerebral cortex and subcortical white matter using standard light microscopic and available immunohistochemical techniques. The remaining specimens could all be classified into one of two broad categories of abnormality. Four patients had multiocular cystic encephalopathy (Fig. 1) involving either the subcortical white matter or the cerebral neocortex, or both. In most, the neuropathological change was indistinguishable from the glial cysts that may represent the residuum of a remote cerebral infarct of cortex or white matter. In patient 8, an 8-month-old girl who underwent a right hemispherectomy, the cystic-gliotic encephalopathy was so severe and associated multifocal dystrophic calcification such a prominent feature that the possibility of cerebral toxoplasmosis was initially considered. However,

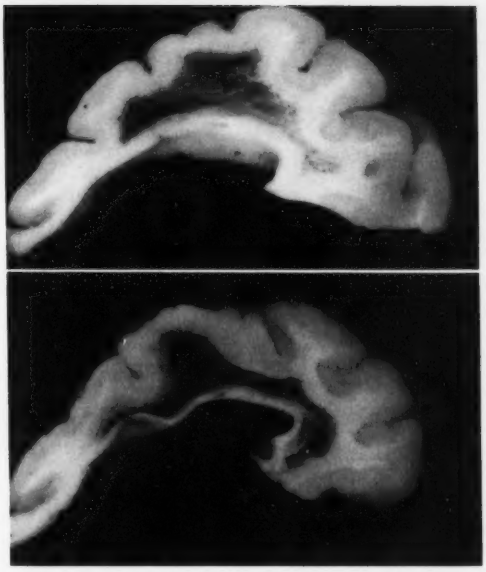

Fig. 1. Patient 2. Coronal sections of brain show large cyst within subcortical white matter, traversed by strands of neuroglial tissue. Ventricular cavity is at bottom of each slice; atrophic corpus callosum is visible at left. Cortical ribbon is relatively well preserved except in the regions nearest the cavity in midportion of each slice

this was ruled out by appropriate immunohistochemical studies using primary antibody directed against *Toxoplasma gondii*. The relative sparing of the occipital region (supplied by the posterior cerebral artery) in the latter patient also tends to support a vascular cause for the encephalomalacic lesions. The destructive lesions in all patients were thought to represent the residua of anoxic-ischemic insults to the brain that had occurred in utero or around the time of birth [14, 15, 38], though the lesions were always so old by histopathological criteria that a precise dating of temporal events important in their pathogenesis could not be ascertained. Occasionally, foci of dysplasia (see below) were noted in brain tissue from patients with coexistent destructive lesions (e.g., patients 3 and 6).

Ten specimens showed abnormalities that were broadly interpreted as dysplastic or hamartomatous in origin [15], though they varied in severity. The individual specimens also showed significant variability in the exact neuropathological features identified (see Table 1) but certain common features were observed. Representative cases will be described and illustrated in detail to highlight this point.

In patient 1, a 17-month-old male, coronal sections of the left hemispherectomy specimen showed effacement of the cortex-white matter junction throughout the temporal lobe (Fig. 2A). On microscopic sections, all regions of the cortex showed a marked abundance of cells which (by routine light microscopy of hematoxylin and eosin-stained sections) showed features of gemistocytic astrocytes, i.e., they had prominent eosinophilic hyaline cytoplasm and usually showed a globoid or oval shape. The globular cells showed variable though focally prominent

Table 1. Neuropathological findings in cortical resection specimens; WM, white matter; GFAP, glial fibrillary acidic protein

Patient no.	Age/sex	Procedure	Cortical dysplasia	Encephalomalacia	Cortical neurofibrillary changes	Other
1	17 months/M	Left hemispherectomy	Temporal lobe grossly, all regions microscopically GFAP-positive globular cells in dysplastic cortex/WM	–	Rare	Heterotopic neurons in WM
2	4 years/F	Left hemispherectomy	–	Cyst in parieto-occipital WM (3.5 cm maximal size) Microscopic changes in frontal lobe	–	Cortical neuron loss overlying cyst; dystrophic (including microvascular) calcification
3	26 months/M	Right hemispherectomy	–	Large cortical glial cyst (old infarct) with macrophages (including some with altered blood pigment), calcification	–	Hippocampus identified, not sclerotic; heterotopic neurons in WM
4	14 months/F	Right parieto-occipital resection	Severe, multifocal, especially superior regions, with enlarged neurons Globular variably GFAP-positive cells in dysplasmic cortex/WM	–	++++ (Frequent interconnecting processes between neurons containing coarse cytoplasmic fibrils)	Focal slight chronic inflammation
5	16 months/F	Left parieto-occipito-temporal resection	Cytoarchitectural neuronal abnormalities including abnormal neuronal "polarity" but no blurring (grossly) of cortex-WM junction	–	–	Prominent astrogliosis, especially subpial and at cortex-WM junction; severe hippocampal sclerosis; heterotopic collections of neurons in WM
6	5 years, 1 month/F	Right hemispherectomy	Focal polymicrogyria	Cystic occipital infarct, calcified	–	Heterotopic neurons in frontal WM
7	33 months/F	Right occipito-temporal resection	Focal polymicrogyria (with loss of synaptophysin immunoreactivity) – associated spongiform change	–	–	Neuronal heterotopias in periventricular WM; focal (including subpial) astrogliosis
8	8 months/F	Right hemispherectomy	–	Severe multifocal cystic change with calcification – relative preservation of occipital lobe	–	–
9	8 months/M	Left parieto-occipito-temporal resection	–	–	–	Essentially normal
10	10 months/F	Right hemispherectomy	Cytoarchitectural abnormalities, slight, especially parietal and temporal (microscopic)	–	–	Rare vacuolated neurons; focal chronic inflammation
11	4.5 months/M	Left parieto-occipital-temporal resection	Severe and widespread with prominent blurring of cortex-WM junction Rare globular cells and spheroids	–	Few	–
12	33 months/F	Right parieto-occipito-temporal resection	Cytoarchitectural disorganization of cortex, especially temporal (microscopic)	–	–	Heterotopic neurons in WM (especially temporal lobe)
13	3 months/M	Left hemisperectomy	Hemimegalencephaly/ hemilissencephaly	–	++++	Prominent multifocal (including perivascular) calcification; periventricular astroglial hamartoma

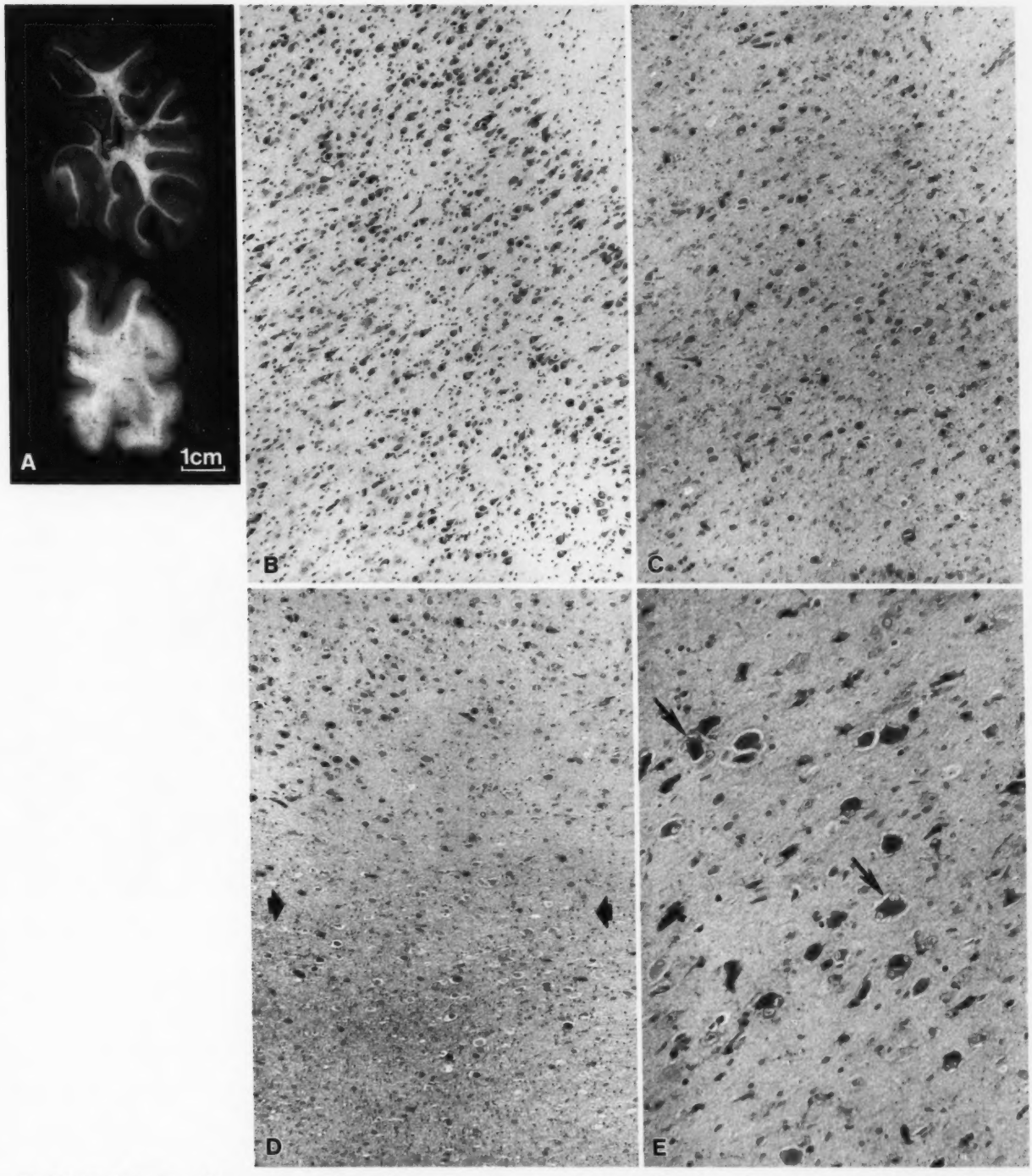

Fig. 2A–E. Patient 1. **a** Two coronal sections of brain from the patient. In some areas, cortex-white matter junction is well-demarcated (*top* of photograph) despite microscopic abnormalities (see Table 1) and both cortex and white matter appear normal. Section of temporal lobe (*bottom*) shows blurring of cortex-white matter junction with overlying tuber-like broad flat gyri. **B, C** Micrographs from parallel sections of identical areas of cortex, **B** from a section stained with Nissl technique, **C** from a section stained with anti-glial fibrillary acidic protein (GFAP). Note pale cells especially prominent in lower left portion of **B**, and abundant variably GFAP-positive cells illustrated in **C**. **D** From the cortex-white matter junction (approximately shown by *arrowheads*, white matter at bottom) in a section stained as for **C**, with anti-GFAP. Note GFAP-positive globular cells scattered throughout both cortex and white matter. **B–D** × 75. **E** Typical appearance of the large globular GFAP-positive cells with characteristic large nuclei and others that are binucleate (*arrows*). Anti-GFAP immunohistochemistry, × 195

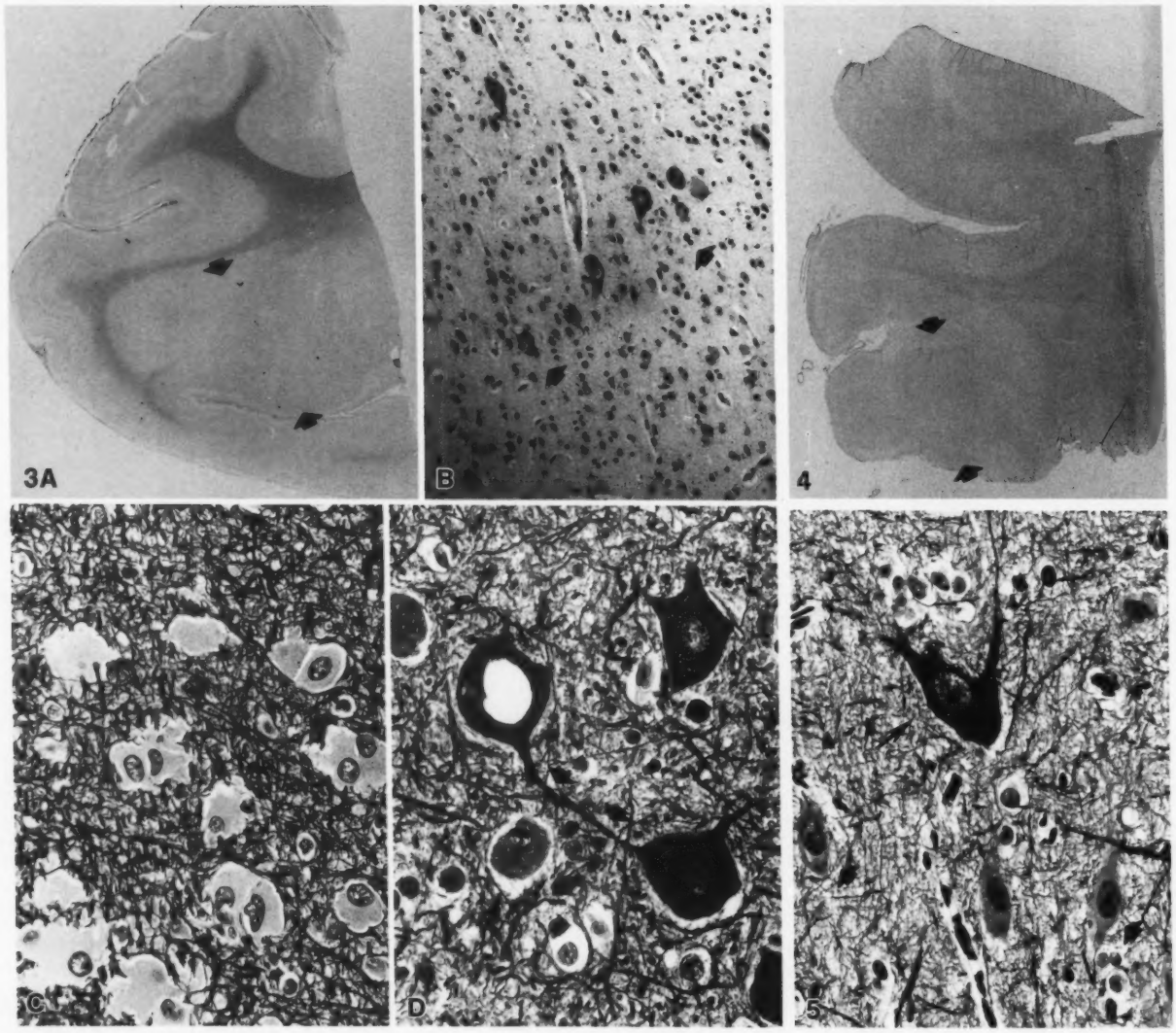

Fig 3A–D. Patient 4. **A** Whole mount section (stained with Kluver-Barrera) shows region of calcarine cortex and adjacent brain. Whereas cortex-white matter junction is normal and cytoarchitectural abnormality is minimal at top of micrograph representing striate cortex, in lower portion of the specimen there is a markedly widened cortical ribbon with blurring of the junction (*arrowheads*) × 5.1. **B** Regions of dysplastic cortex indicated by *arrowheads* in **A**, with scattered neurons showing enlarged cell bodies and abnormal polarity (*arrows*). Kluver-Barrera stain, × 215. **C, D** Globoid cells (**C**) similar to those illustrated in Fig. 2 (stained with the Bielschowsky silver technique). These were seen in close proximity to atypical neurons containing dense neurofibrillary accumulations and occasional cytoplasmic vacuoles (**D**). Both neurons show barely visible nuclei largely obscured by the coarse neurofibrils. Neuronal cell body with relatively normal cytoplasm is shown by *arrow*. Note abnormal inter-neuronal communication (indicated by *arrowheads*). **C** × 500, **D** × 785

Fig. 4. Patient 11. Kluver-Barrera stained section of cortex shows blurring of cortex-white matter junction and severely dysplastic cortex with irregular, sometimes fused gyri and marked focal widening of the cortical ribbon (e.g., indicated by *arrowheads*). × 5.0

Fig. 5. Patient 13. Representative section of "cortex" (cortex and white matter were essentially indistinguishable). Note prominent cytoskeletal disorganization, coarse intracytoplasmic neurofibrillar structures indicated by *arrow*. *Arrowheads* indicate neurons with relatively normal cytoplasm. Bielschowsky stain, × 545

GFAP immunoreactivity (Fig. 2b–e). These cells were frequently binucleated or contained multilobulated nuclei and were prominently distributed at the cortex-white matter junction, but extended into the superficial white matter and into the cortex throughout all regions of the resected brain. The microscopical change was most pronounced in the temporal lobe, where gross abnormalities had been identified. On Bielschowsky-stained sections, collections of coarse cytoplasmic neurofibrils resembling early neurofibrillary tangle formations were seen within neurons of the most dysplastic regions of cortex. In patient 4, a 14-month-old female who underwent a right

parieto-occipital resection, prominent neuronal cytomegaly was seen within severely disorganized and dysplastic cerebral cortex (Fig. 3). The cortical disorganization was visible even on cut sections of the brain and appropriately stained whole mounts. Globular cells similar to those identified in patient 1 were present throughout the dysplastic cortex and in the superficial white matter (Fig. 3). In the disorganized neuronal layers throughout the cortex and in the superficial white matter, abundant neurons with coarse cytoplasmic neurofibrils were identified as were enlarged neurons, and cytoplasmic vacuolization was prominent. Often, abnormal processes containing tangle-like material were seen connecting adjacent neuronal cell bodies (Fig. 3D).

In patient 11, a 4.5-month-old male who underwent a left parieto-occipito-temporal resection, there was severe and widespread cortical dysplasia with pronounced widening of the cortical ribbon in many areas (Fig. 4) and rare globular cells (as described above) were identified in the cortex and white matter. In patient 13, a 3-month-old male who underwent left cerebral hemispherectomy, sections of the cut brain revealed virtually total absence of secondary sulci and gyri, giving an appearance of lissencephaly or pachygyria [15], though similar changes have been described as "hemimegalencephaly" [30, 55]. Also, cut sections of all areas of the cortex revealed that there was no distinction of the cortex-white matter junction, and all areas of the cortex were extremely firm to palpation. Microscopically, there was extreme disorganization of all regions of the neocortex and absence of even a semblance of cortex-white matter junction. No lamination of neurons was seen in the cortex. Individual neurons showed cytomegaly and displacement of Nissl substance to the periphery of the neuronal cell bodies. Marked astrocytic gliosis and multifocal punctate and perivascular calcification was also identified throughout the brain parenchyma. Bielschowsky-stained sections of many regions of the cortex demonstrated abundant neuronal collections of coarse neurofibrils among the misplaced and maloriented neuronal cell bodies (Fig. 5). Ultrastructural assessment of cortex from this patient showed abundant cytoplasmic intermediate filaments and elongated electron-dense rods with a discernible crystalline substructure (Fig. 6); the morphology and size of these rod-like bodies was virtually identical to that previously described in cerebral lesions from patients with tuberous sclerosis (TS) [2]. Paired helical filaments were not seen in any cell.

Immunohistochemical studies

Synaptophysin immunohistochemistry was routinely used to assess the presence of synaptic protein or of neuronal differentiation within cerebral cortex and within neuronal clusters of the subcortical white matter. Of interest was the observation that, when heterotopic disorganized collections of neurons were seen deep within the subcortical white matter, these collections of cells stained almost as prominently as the overlying cortex (Fig. 7A), suggesting synaptic development within these foci. The simple presence of synaptophysin does not, however, necessarily imply previous physiological activity of the synapses in the viable cortex prior to resection. Synaptophysin immunocytochemistry was also used to assess the integrity of the cortical ribbon. For example, when focal cortical dysplasia or polymicrogyria was identified, synaptophysin immunohistochemistry could be used to demonstrate that there was a gradual but profound loss of immunostaining within the dysplastic cortex as compared to adjacent normally organized areas (Fig. 7B, C). The globular cells described showed variable immunoreactivity for GFAP and synaptophysin. Of even greater interest were the results of sequential dichromatic immunohistochemistry, using first antibodies to synaptophysin and secondly antibodies to GFAP, to assess the nature of the cells frequently observed as a hamartomatous proliferation within the cortex and subcortical white matter. When separate immunocytochemical studies were done, it was clear that some of the cells within dysplastic cortex showed variable immunoreactivity for GFAP (e.g., see Fig. 2), whereas others showed variable immunoreactivity for synaptophysin. When double-labeling techniques were applied, many of the cells were seen to contain both neuronal and astrocytic epitopes (Fig. 8).

Neurofibrillary tangle-like accumulations of coarse cytoplasmic neurofibrils were seen within neurons of the cortex (especially malformed cortex) in several patients (most prominent in patients 4 and 13). Preliminary immunocytochemical studies indicate that these cells are positive for Alz 50 protein [25, 51] and negative for the Alzheimer A4 or beta-peptide, the latter assessed using techniques employed in ongoing work in our laboratory [58, 59]. Obviously, it would be of interest to know whether these tangles contain epitopes similar to those seen in neurofibrillary tangles commonly observed in the neocortex and hippocampus in patients with Alzheimer's disease.

Discussion

Autopsy studies have shown that the neuropathological substrate of infantile spasms is heterogeneous, as may be that of various forms of primary generalized epilepsy in children and young adults [3, 20, 27, 34, 35, 39, 41, 44, 50, 53, 54]. Developmental and destructive forms of neuropathological change may coexist in one and the same brain. Jellinger has classified brain abnormalities that may lead to infantile spasms as "embryofetal lesions" including malformations and developmental disorders, hamartomatous malformations (including variants of TS), metabolic disorders (including leukodystrophies, neurolipidoses, and amino-acidopathies), perinatal and postnatal encephalopathies, and vascular or inflammatory cerebral disorders [27]. Occasionally, perinatal destructive lesions may be superimposed on a malformed brain, as we have also noted. In approximately 4–5% of cases examined at necropsy, no specific neuropathological finding is identified. Previous studies have been based almost exclusively on postmortem examinations, and few immunohistochemical or ultrastructural investigations of

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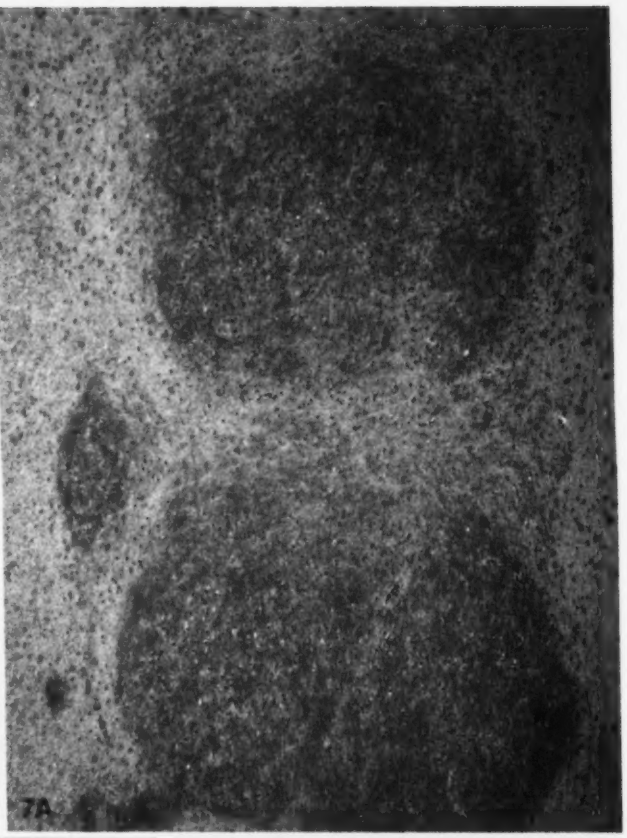
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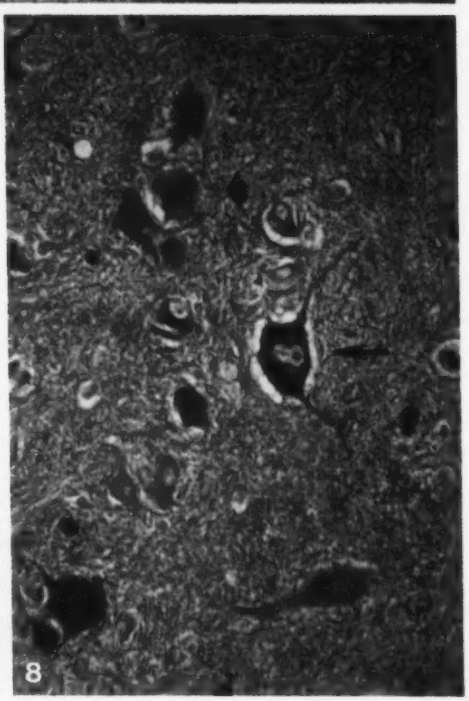
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the underlying neuropathological change have been carried out.

We have had the unique opportunity to study 13 large cortical resection specimens removed in the course of hemispherectomy [21] or multilobar resection for the treatment of medically intractable infantile spasms. Many of the specimens have been studied by electrophysiological techniques, allowing for eventual correlations of neuronal structure and function in the epileptic human (juvenile) brain [63]. Routine neuropathological study of the material has yielded several interesting abnormalities. In general, however, virtually all patients showed either malformative lesions or encephalomalacic lesions or a combination of the two. Malformative lesions included large heterotopic collections of neurons within the subcortical white matter, severe focal cortical dysplasia or polymicrogyria, and hemimegalencephaly (usually with neuronal cytomegaly) or hemi-lissencephaly [4, 8, 11, 12, 18, 29, 40, 49]. The authors accept the fact that "Focal cortical dysplasia" is as yet an inaccurate and less than satisfactory term. For instance, some investigators describe subtle malformative cortical abnormalities as "microdysgenesis" [35].

Of special interest in terms of immunohistochemical study were the large globular ("balloon") cells identified, particularly at the cortex-white matter junction and widely distributed throughout the brains of patients 1 and 4. In the same patients, silver-stained sections sometimes showed prominent coarse neurofibrillar collections within cell bodies that were frequently seen adjacent to the globular cells, and these neurons often showed interconnecting cellular processes that themselves demonstrated accumulations of neurofibrils. Neurofibrillary tangles resembling the cytoplasmic changes we describe are seen in the neocortex and hippocampus of patients with Alzheimer's disease (AD) or senile dementia of Alzheimer type (SDAT), though numerous studies have indicated that they are by no means specific to this disorder [19, 23, 28, 57]. Neurofibrillary change has been reported in the cortical tubers of patients with TS, where granulovacuolar degeneration and Pick-like bodies may also rarely be seen [22]. Preliminary ultrastructural examination suggests that these intracytoplasmic neurofibrillary tangles are composed of straight or curving intermediate filaments, unlike the paired helical filaments identified in the neuronal cell bodies containing neurofibrillary tangles from patients with AD or SDAT [57]. The finding of these cytological changes within neuronal cell bodies raises, however, the possibility that neurofibrillary degeneration or accumulation of coarse fibrils may be a nonspecific sequela of neuronal cell body injury or "disconnection" of synapses, as suggested in other contexts [16, 57]. We have also observed widespread neocortical neurofibrillary tangle-like changes in large cortical resections that have been undertaken for the treatment of other epileptic disorders in the pediatric age group [62].

Focal cortical dysplasia or microdysgenesis as a cause of epilepsy has previously been described in children and young adults [35, 52]. Rarely, cortical dysplasia may manifest as diffusely thickened cortex-possibly a *forme fruste* of lissencephaly [31]. Detailed study of specimens removed from patients with focal neocortical dysplasia showed widening of the cortex with abnormal neuronal cortical layering and proliferation of large, frequently bizarre neuronal and astrocytic cells [52]. The junction between normal cortex and severely dysplastic cortex was frequently noted to be fairly abrupt [52]. The possibility has been raised that this focal cortical dysplasia represents a variant of TS, though focal cortical dysplasia has been thought to show sufficient distinguishing features from TS (both in its clinical and pathological manifestations) to consider it a separate entity. Nevertheless, in several of our patients the focal cortical abnormalities with blunting of the cortex-white matter junction, severe cortical disorganization, proliferation of giant neuronal cell bodies and widespread distribution of globular variably GFAP-positive cells suggest a kinship between this form of focal cortical abnormality and the tubers identified in the neocortex of patients with TS, as well as other hamartomatous lesions encountered in this phakomatosis [6, 7, 24, 26, 37, 43, 56]. The relationship is also suggested by the ultrastructurally similar crystalline structures noted in the cell cytoplasm, though the origin and significance of these is currently unknown [2]. Although extensive cortical resections have been undertaken in our patients, and the ventricular surfaces (when present in the specimen) have been carefully examined, neither subependymal giant cell tumors nor other subependymal lesions characteristic of TS have been identified, though patient 13 may represent an exception to this. There is no evidence that the developmental neocortical abnormalities that we describe are familial, though detailed assessment (using neuroimaging and genetic techniques) of the families form which the patients in our study originated have not as yet been undertaken.

Immunohistochemical study, particularly of the globular and other atypical cells described, also indicates that they are similar to those frequently observed in the cortical tubers and subependymal giant cell tumors of TS, which show both neuronal and astrocytic epitopes [36,

Fig. 6. Ultrathin section from cortex of patient 13. Neuronal cytoplasm shows rod-like crystalline structures in close proximity to rough endoplasmic reticulum. Intermediate filaments (*arrow*) are seen adjacent to the nucleus. Uranyl acetate, lead citrate, ×29,600

Fig. 7. **A** Patient 5. Heterotopic collections of neurons in subcortical white matter stained using immunoperoxidase technique, with primary antibody to synaptophysin. Reaction product is visible overlying large and small collections of neurons. ×90. **B, C** From parallel sections of calcarine cortex (patient 7) stained with Kluver-Barrera (**B**) and anti-synaptophysin (**C**). Note that region of focal cortical dysplasia/polymicrogyria (*arrow* in **B**) shows loss of synaptophysin immunoreactivity (*arrow* in **C**), whereas intact cortex (lower region, **C**) demonstrates normal immunoreactivity. **B** ×4.3; **C** ×3.3

Fig. 8. Patient 13. Hemimegalencephaly. Dichromatic immunohistochemistry carried out using anti-GFAP (glucose oxidase technique, blue reaction product) and anti-synaptophysin (brown reaction product). Note that some cells show only blue reaction product indicating GFAP (*arrowhead*), whereas in other cells there is cytoplasmic co-localization of the antigens (*arrow*). ×455

46–48]. Our studies indicate that some cells have both synaptophysin and GFAP within their cytoplasm. These studies suggest that the proliferating cells present primitive or multipotential neuroectodermal elements within the white matter and deep cortex. They may represent elements that have differentiated abnormally following incomplete migration from the germinal matrix to the cortical mantle, though the reasons for their abnormal location and bizarre morphology are unclear from this study. Of further interest is the finding that synaptophysin immunohistochemistry could be used to confirm the presence of synaptic markers (though not necessarily physiologically active synapses) within clusters of heterotopic neurons within subcortical white matter, when these were present in resected cerebral specimens. Furthermore, as illustrated in patient 7, regions of polymicrogyria frequently showed a diminution in synaptophysin staining when staining intensity was compared with adjacent normal neocortex. Further refinements of immunohistochemical and in situ hybridization techniques may be used to study the embryonic origins of dysplastic cerebral lesions in greater detail.

The evidence for efficacy of cortical resection in the treatment in infantile spasms suggests that the morphological and structural lesions observed are largely focal or predominantly located within one cerebral hemisphere [5]. Studies in affiliated laboratories are currently in progress aimed at assessing electrophysiological parameters within brain sections adjacent to those that have been subjected to the morphological studies described above [63]. It is conceivable that electrophysiological recording can be made from neurons or primitive neuroectodermal cells, which can subsequently be examined using conventional light microscopic or immunohistochemical techniques following in vitro labeling of the cell bodies. Long-term assessment of developmental parameters in surgically treated and "control" patients is also essential for accurate assessment of efficacy of the surgical procedures.

The developmental abnormalities identified (e.g., unilateral megalencephaly, focal cortical dysplasia with hamartomatous proliferation of globular cells, focal polymicrogyria) probably arise form one or more of several insults to the developing nervous system that occur in utero [15, 42]. The result may be aberrant neuronal migration to and lamination within the cerebral cortical mantle [1, 33, 45]. It is not surprising to find the coexistence of developmental and destructive lesions [most likely secondary to anoxic-ischemic damage) within one and the same cerebral specimen. The latter may occur later in gestation after neuronal migration is relatively complete. Further study of these unusual neuropathological abnormalities may yield important clues to the cellular and molecular neuropathogenesis of infantile spasms and other forms of focal or generalized epilepsies [9, 10].

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Effects of congenital hydrocephalus on serotonergic input and barrel cytoarchitecture in the developing somatosensory cortex of rats

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Abstract. The effects of progressive ventricular dilation on the development of the somatosensory cortex (SmI) were studied in congenital hydrocephalic rats, with regard to early serotonergic innervation and formation of functional cellular columns. In hydrocephalic rats, the time course, immunoreactivity, and patterns of formation and synaptogenesis of serotonin immunoreactive (5-HT-IR) terminal aggregations, which characterize the development of the SmI, were preserved. After disappearance of 5-HT-IR terminals, characteristic barrel cytoarchitecture formed normally at the site where 5-HT-IR terminal aggregations had been present. With the progression of hydrocephalus, the cerebral cortex became extremely thin and its total surface area was greatly increased, while barrels were preserved and their areas did not enlarge. These findings suggest that the basic development and the fundamental cytoarchitecture of the cortex are resistant to adverse effects of hydrocephalus.

Key words: Hydrocephalus – Serotonin – Barrel cytoarchitecture – Rat cortex – Synaptogenesis – Monoamine neurons

Many reports have been published on the pathology and pathophysiology of experimental hydrocephalus. Most of them used models of acquired hydrocephalus. On the other hand, there are fewer studies of congenital hydrocephalus, particularly with regard to the early development of the cerebral cortex. In animals with congenital hydrocephalus, it seems probable that the brain is adversely affected by hydrostatic pressure throughout the prenatal and perinatal periods, which are the most important stages in normal development of the cerebral cortex. Unlike acquired hydrocephalus, therefore, secondary developmental disturbance of the cerebral cortex may occur in congenital hydrocephalus.

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Many previous studies indicated that monoamine neurons play an important role in the early development of the cerebral cortex [4–7, 13–15, 18, 21]. Accordingly, investigations of monoamine neurons in congenital hydrocephalus would seem to be important, but there have been few such studies [1, 3, 11].

Among monoamine neurons in rats, serotonin (5-HT) neurons have a characteristic pattern of development [2, 6, 7, 15, 18]: namely, they form transient terminal aggregations in the somatosensory cortex (SmI) early in the postnatal life (Fig. 1C). In layer IV of the SmI in rat, there is a characteristic cytoarchitectural feature called a "barrel," which represents a functional column of the a map of the rat body and correspond with the peripheral/surface somatotopic distribution (Fig. 1B) [20]. The 5-HT terminals aggregate where the barrels eventually develop (Fig. 1A, C, D) [18]. Accordingly, we thought that early 5-HT input to the SmI was closely related to its normal development.

In the present experiments, we used immunohistochemical methods to study the development of 5-HT input in the cerebral cortex of congenitally hydrocephalic rats early in postnatal life. We also studied the barrel cytoarchitecture of the SmI, which followed the transient aggregation of 5-HT terminals, to determine the influence of hydrocephalus after the initial cortical development.

Materials and methods

Experiments were conducted in strict adherence to the *Standards of Animal Experiment and Animal Care* of our institution.

Sprague-Dawley (SD) rats with hydrocephalus induced by transplacental administration of ethylnitrosourea, and albino congenitally hydrocephalic rats (HTX) were used [9, 17].

For transplacental induction of hydrocephalus, an intraperitoneal injection of ethylnitrosourea (25 mg/kg) was given to pregnant SD rats on the 10th day of gestation. The degree of hydrocephalus varied from mild to severe in both types of congenital hydrocephalus. Only those rats showing marked cranial enlarge-

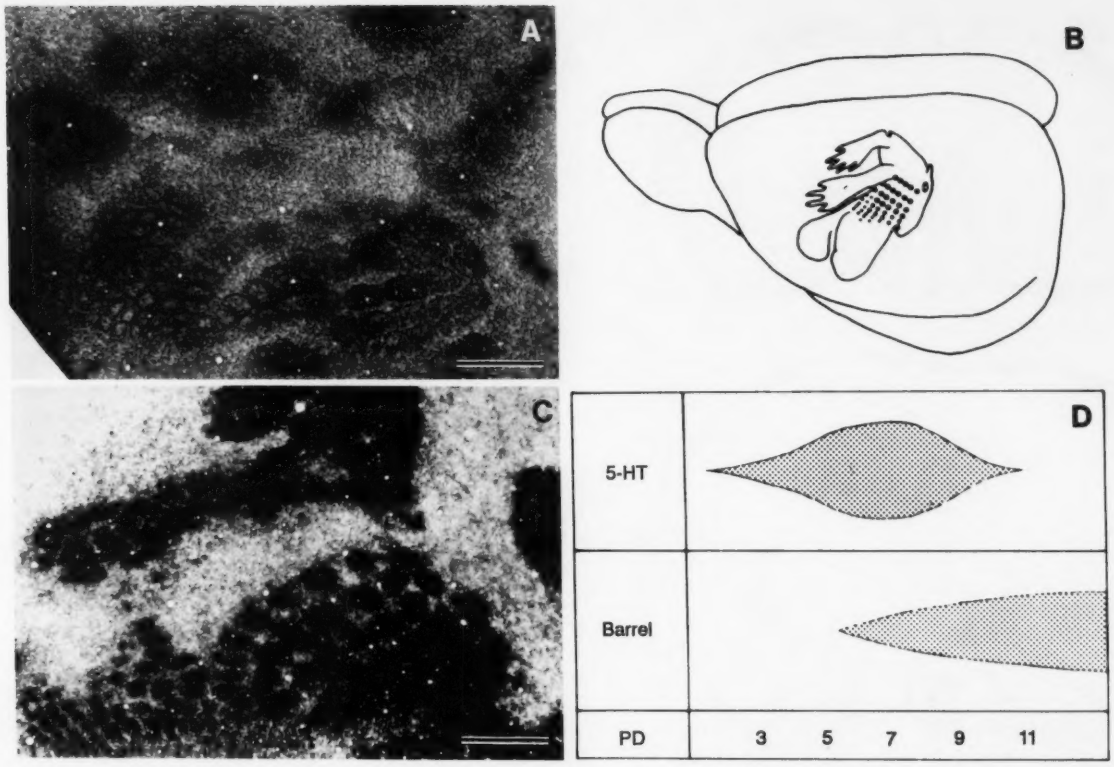

Fig. 1. **A** Tangential section of the rat SmI on PD 14 stained with gallocyanine. × 13; *bar* 1 mm. **B** Schematic drawing of the rat SmI (modified from [20]). *Closed circles* show the region called PMBSF. **C** Tangential section of the rat SmI on PD 7 stained by the 5-HT immunohistochemical technique. × 13; *bar* 1 mm. **D** Schematic representation of the development of 5-HT-IR terminal aggregation and barrel

ment and cortical thinning were used for the experiments. The severity of hydrocephalus did not differ significantly between the two hydrocephalus types (Fig. 2). When untreated, such animals died spontaneously 4–5 weeks after birth. Nonhydrocephalic littermates served as controls.

Deep anesthesia was induced with an intraperitoneal injection of pentobarbital sodium on postnatal day (PD) 3, 5, 7, 9, or 11 (first 24-h period after birth being counted as PD 1), or 2, 3, 4, or 5 weeks after birth. After preliminary perfusion with phosphate-buffered saline (pH 7.4) via the heart, perfusion-fixation was performed for 10 min with ice-cold 0.1 *M* phosphate buffer containing 4% paraformaldehyde, 0.5% glutaraldehyde, and 0.2% picric acid. The brain was removed and postfixed for 2 days, and then immersed in 0.1 *M* phosphate buffer containing 15% surcrose for 2 days.

The cerebral cortex of the dorsolateral convexity on one side was resected and serial cryostat sections were prepared parallel to the pial surface (tangential section). Twenty-micrometer-thick sections were stored in phosphate-buffered saline containing 0.3% Triton-X 100 and 0.1% sodium azide for at least 4 days and processed for 5-HT immunohistochemistry. The specificity of the antiserum has been described previously [19]; it crossreacted only with 5 hydroxytryptophan at a level of less than 0.1%. Eighty-micrometer-thick sections were stained with gallocyanine. The cerebral hemisphere on the opposite side was cut coronally and stained with gallocyanin to examine the severity of ventricular dilation and cortical thinning.

The area with five rows of barrels corresponding to the mystacial vibrissae, i.e., the posteromedian barrel subfield (PMBSF) of Welker [20], was measured using a camera lucida drawing of the gallocyanine-stained tangential section (Fig. 5A, C). The distance between the interventricular foramen and layer IV of the SmI was measured using a coronal section of the opposite cerebral hemisphere, and defined as a ventricular radius (Fig. 5E). The relationship between the area of the PMBSF and the ventricular radius was examined in HTX hydrocephalic and control rats 2–5 weeks after birth.

In HTX rats, an electron-microscopic study of 5-HT terminals was also performed. The 5-HT immunoreactive (-IR) synapses were classified by their synaptic profiles and the synaptogenic tendencies in hydrocephalic HTX and control rats compared.

Results

5-HT terminal aggregations in hydrocephalic and control rats

In the rat SmI, there is a characteristic transient 5-HT terminal aggregation [2, 6, 15, 18]. The 5-HT-IR fibers were scattered in the subplate on PD 1 and entered the cortical plate at its basal side on PD 2. On PD 3, they formed lumps with accompanying numerous 5-HT-IR terminals, and were distributed roughly in the shape of the SmI. The 5-HT-IR terminals progressively increased in number from day 3 and formed terminal aggregations which exactly corresponded to the somatotopic cytoarchitecture (see Fig. 1). Each segment of the 5-HT-IR terminal aggregations was clearly observed on PD 5 and

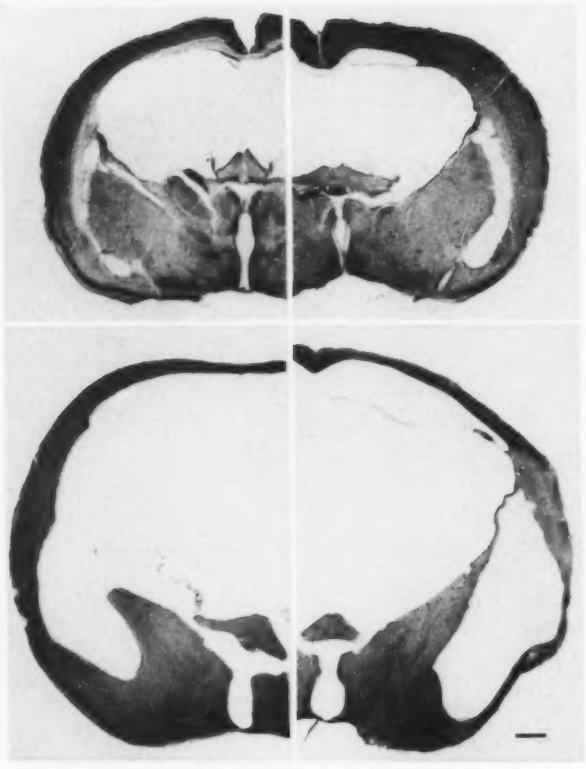

Fig. 2. Photomicrographs of coronal sections from HTX and ethylnitrosourea- (ENU-) induced hydrocephalic rats. The degree of hydrocephalus is almost the same in these two kinds of hydrocephalic rats. *Top* PD 14; *bottom* PD 28; *left* ENU-induced hydrocephalic rat; *right*, HTX hydrocephalic rat. ×4; *bar* 1 mm

their density peaked on PD 7. Thereafter, the density decreased and the terminal aggregations disappeared on PD 11 (see Fig. 1 D).

We studied the pattern of development of these aggregations in congenitally hydrocephalic rats and compared it to that in control animals. Since light-microscopic findings did not differ significantly between two types of hydrocephalus, these are described together.

On PD 5, the aggregations were seen in hydrocephalic rats as clearly as in control rats. Their intensities peaked on PD 7 in both hydrocephalic and control rats and decreased thereafter. The aggregations in the area of the PMBSF had disappeared by PD 11 in control rats, while in both types of hydrocephalus they were still observable, though faintly, at that date. In general, the formation and transient nature of 5-HT input to the SmI were well-preserved in hydrocephalic rats, although the disappearance of the terminal aggregations was slightly delayed (Fig. 3).

The 5-HT-IR terminals were examined electron-microscopically in HTX rats in order to study their functional development. Two types of synaptic contacts, axosomatic and axodendritic, and two types of synapses, asymmetrical and symmetrical, were all observed similarly and equally in hydrocephalic HTX and control rats (Fig. 4). To compare synaptogenic tendencies, the numbers of observed terminals were tabulated according to the type and site of synapse (Table 1). There were no differences between hydrocephalic HTX rats and controls with regard to the ratio of asymmetrical to symmetrical synapses, the ratio of axosomatic to axodendritic contacts, or the ratio of numbers of synapses between the cortical plate and the subplate. These data indicate that the synaptogenesis of 5-HT-IR terminals is well-preserved in HTX hydrocephalic rats.

Barrel cytoarchitecture in the PMBSF of HTX hydrocephalic and control rats

Barrel formation lagged behind that of 5-HT-IR terminal aggregations and became apparent in the 2nd week after birth (see Fig. 1 D). To investigate the influence of hydrocephalus on SmI after the initial stage of cortical development, barrels of congenitally hydrocephalic rats after the 2nd postnatal week were compared with those of control rats.

Four to 5 weeks after birth, ventricles were markedly dilated in hydrocephalic rats. The cerebral cortex had been smoothly and markedly flattened and thinned with no abrupt or focal changes in thickness (Fig. 5 E). In the coronal section through the interventricular foramen, cortical neurons were maximally flattened, decreased in number, and their long axes, which are normally perpendicular to the pial surface, were now parallel to it (Fig. 5 F).

Despite such a severe hydrocephalus, however, five rows of large barrels in the PMBSF were still clearly seen in the tangential section (Fig. 5 C). In addition, the area of the PMBSF was not larger in hydrocephalic rats than in controls (Fig. 5 A), despite a marked increase in the whole surface area of the cortex.

The surface areas of the PMBSF of 10 HTX control and 12 HTX hydrocephalic rats were plotted against the squares of the ventricular radius, because an increase in the whole area of the cerebral cortex in hydrocephalic rats is expected to be roughly proportional to the square of the ventricular radius (Fig. 6). Shrinkage or expansion of specimens during fixation, sectioning, and staining was below 5%. The PMBSF area in hydrocephalic rats remained unchanged until the square of the ventricular radius reached 60–80 mm^2, a value twice as large as in controls (30–40 mm^2). The PMBSF area was only slightly larger even when the square of the ventricular radius exceeded 80 mm^2 and reached 90–120 mm^2, which is three times as large as the control value (Fig. 7).

In addition, the spatial organization of layer IV in tangential sections was compared between hydrocephalic and control rats, using the PMBSF and the visual field as landmarks (Fig. 5). It became evident that the distance between the PMBSF and the visual field was markedly increased in hydrocephalic rats, the less cellular cortex between the PMBSF and the visual cortex having been strikingly stretched out. The results indicate that a certain part of cerebral cortex was more vulnerable than other parts, and that the PMBSF and its fundamental cytoarchitectural units were highly resistant to stretch caused by progressive ventricular dilation and increasing hydrostatic pressure.

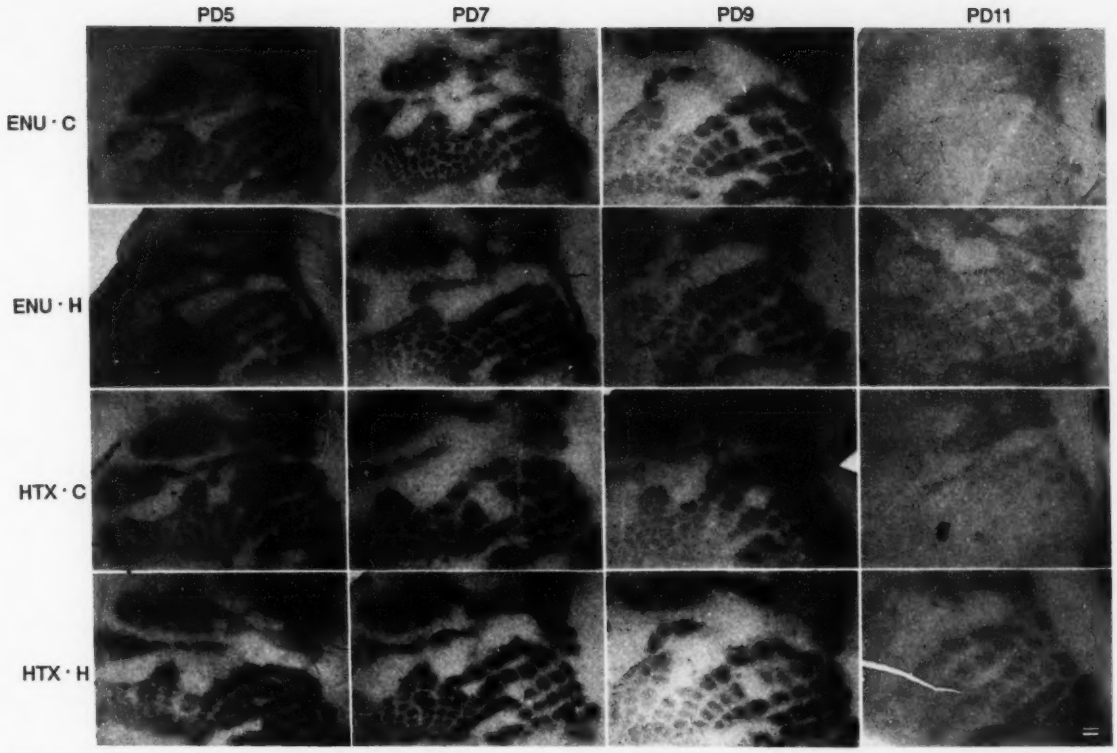

Fig. 3. Comparison of the time course of 5-HT-IR terminal aggregations between hydrocephalic rats and control. The disappearance of the aggregations is sightly delayed in both groups of hydrocephalic rats, whereas the characteristic transient formations are preserved. *ENU · C*, ENU control rat, *ENU · H*, ENU hydrocephalic rat, *HTX · C*, HTX control rat, *HTX · H*, HTX hydrocephalic rat. ×2.2; *bar* 1 mm

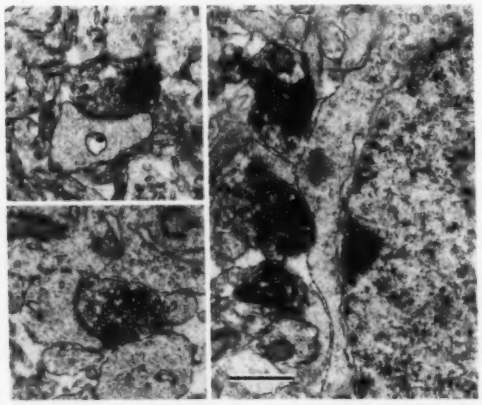

Fig. 4. Electronmicrographs of 5-HT-IR terminals, showing normal development of symmetrical (*left upper*) and asymmetrical (*left lower*) axodendritic synapses and axosomatic synapses (*right*) in an HTX hydrocephalic rat. *Bar* 5μm

Table 1. Comparison of development of 5-HT-IR terminals between HTX hydrocephalic and control rats. Values in brackets are of asymmetrical synaptic profile. There are no apparent differences in synaptogenesis between hydrocephalic and control rats. AS, Axosomatic contact; AD, axodendritic contact; CP, cortical plate; SP, subplate

			Postoperative day				
			3	5	7	9	11
Control	CP	AS	3 (1)	4 (0)	19 (2)	1 (0)	1 (1)
		AD	14 (6)	26 (12)	86 (39)	113 (56)	75 (48)
	SP	AS	6 (1)	6 (0)	1 (0)	0 (0)	1 (0)
		AD	24 (10)	34 (14)	19 (9)	31 (13)	71 (46)
Hydrocephalus	CP	AS	5 (0)	7 (1)	13 (0)	1 (0)	2 (0)
		AD	13 (4)	64 (35)	155 (67)	95 (52)	60 (31)
	SP	AS	1 (0)	11 (4)	2 (0)	4 (0)	3 (2)
		AD	9 (4)	36 (21)	18 (6)	36 (15)	47 (22)

Discussion

In the SmI of rat, there is a characteristic development of transient serotonergic terminal aggregations [2, 6, 7, 15, 18]. Early in postnatal life, the 5-HT-IR fibers and terminals are already aggregated in the shape of the future SmI in the subplate before establishment of cortical lamination. These fibers then form dense aggregations with the development of cortical cytoarchitecture, and finally decrease with maturation. The 5-HT-IR terminals aggre-

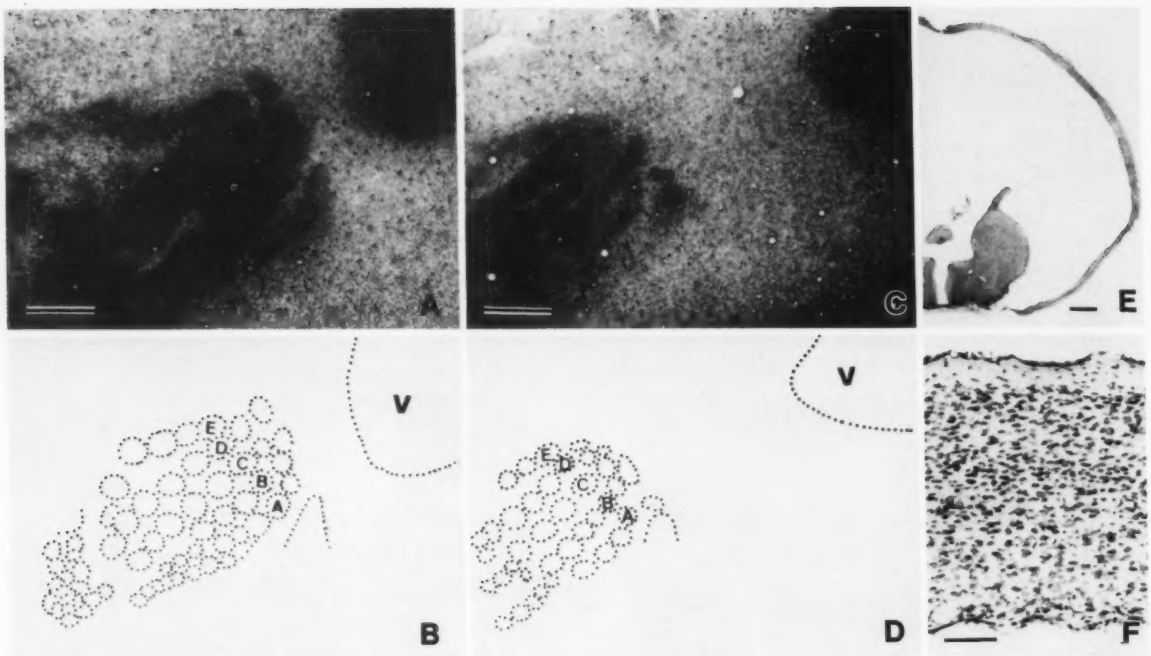

Fig. 5. **A, C** Photomicrographs of tangential section from a control (**A**) and an HTX hydrocephalic (**C**) rat on PD 35. **B, D** Schematic drawings of **A** and **C**, respectively. The coronal section from the opposite side (**E**) shows marked dilation of the ventricle, cortical thinning, and flattening of cortical neurons (**F**), while the PMBSF area is not enlarged. *V*, Visual field. **A, C** ×10; **E** ×4; **F** ×80; *bar* 1 mm in **A, C, E**; 100 μm in **F**

Fig. 6. Sagittal (*left*) and coronal (*right*) sections from brains of an HTX control rat (*top*) and an HTX hydrocephalic rat (*bottom*). In the hydrocephalic rat, the cerebral cortex is markedly stretched in both the rostrocaudal and the mediolateral direction. ×2.6; *bar* 1 mm

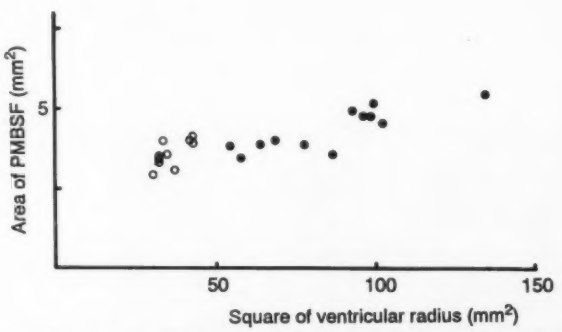

Fig. 7. Relationship between the area of PMBSF and the square value of the ventricular radius. In the face of marked enlargement of the ventricular radius, the area of the PMBSF of hydrocephalic rats remained stable and was quite limited even when the square of the radius was three times as large as in controls. *Open circles* HTX control rats ($n=10$), *filled circles* HTX hydrocephalic rats ($n=12$)

gated in the hollow part of the barrel where the thalamocortical afferents densely terminate [8, 18]. These facts strongly suggested that 5-HT plays an important role in the development of the SmI of rat.

In the rat fetus, 5-HT-containing cells of the raphe nuclei begin differentiating on embryonic days 11–15 [10]. The main ascending axon bundles of these 5-HT neurons reach the cerebral cortex either medially through the septum and the diagonal band or laterally through the striatum [7]. Thus, the 5-HT input to the cerebral cortex is an extrinsic innervation taking a long ascending course. In rats with congenital hydrocephalus, it might be expected therefore that increased hydrostatic pressure associated with progressive enlargement of the ventricles would adversely affect the development of such long ascending pathways from the late fetal period. Furthermore, such a disturbance of 5-HT input might then dis-

turb normal cerebral cortical development. In fact this hypothesis is supported by recent studies of the changes of monoamine neurons in neonatal acquired hydrocephalus induced by cisternal injection of kaolin early in postnatal life [1, 11]. Chovanes et al. [1], studying kaolin-induced neonatal hydrocephalic rats at 12 days after birth, reported that norepinephrine and dopamine in the cerebrum and 5-HT in the cerebellum were decreased and norepinephrine and 5-HT were increased in the brain stem. Lovely et al. [11] reported similar results in kaolin-induced hydrocephalic cats at 7 to 8 weeks. These results are similar to those of Ehara et al. [3], who studied kaolin-induced hydrocephalus in adult rats.

Contrary to the results of acquired hydrocephalus, however, the characteristic development of transient 5-HT innervation of the SmI was clearly observed in congenital hydrocephalic rats in the present study. No essential differences were found between hydrocephalic rats and control rats as to the time course of 5-HT innervation, distribution of 5-HT input, its immunoreactivity, and synaptogenesis of 5-HT-IR terminals. This is different from previous studies which showed impairment of axonal transport and/or of the ascending pathway. This difference may have been caused in part by the use of kaolin, which can directly affect the brain stem function, while the prime cause was the difference in experimental subjects. Previous reports studied adult-like innervation in the animals in the maturational stage while we studied transient innervation early in development. In the present study, the transient 5-HT input was unaffected in both models of congenital hydrocephalus, suggesting that the early functional development of the cerebral cortex was well preserved in the face of marked ventricular dilation. It seems, therefore, that these types of congenital hydrocephalus may well be reversible, in the sense that they are not accompanied by primary maldevelopment of the brain.

By late in the 2nd week after birth, the 5-HT-IR terminal aggregation had disappeared, whereas the barrel cytoarchitecture became progressively more distinct, taking the place of the terminal aggregations on tangential sections [15, 18]. The distribution of barrels and other cellular aggregations represents the body shape of rats, as shown by electrophysiological studies [20]. In the PMBSF, barrels are arranged in five rows, like the rows of the mystacial vibrissae, and each barrel corresponds exactly to a single vibrissa [20].

The barrels were astonishingly well preserved and the whole area of the PMBSF was scarcely enlarged in the brain of hydrocephalic rats aged 4–5 weeks, even though the pallium was extremely thin, white matter was hardly visible, and the cortical neurons were flattend and their long axes were parallel to the pial surface. When compared to other parts of the cerebral cortex, the PMBSF was very resistant to stretching (Fig. 5). In other words, the vulnerability of the cortex to progressive ventricular dilatation was not uniform.

In clinical practice, it is not unusual to see patients with high-grade hydrocephalus in whom motor and/or sensory functions are well preserved while other cortical functions are severely compromised. Assuming that the structural changes in the cortex are reflected in neurologic symptoms, differences in the vulnerability of the cortex as seen in this study might explain such a dissociation of symptoms, at least in part, although admittedly direct extrapolation of experimental results in rodents to clinical cases has to be done most prudently.

From these findings, we conclude that the basic development and fundamental cytoarchitecture of the cerebral cortex are resistant and continue to develop despite hydrocephalus, even if the ventricular dilatation occurs before the cortical lamination. In regard to cortical development, congenital hydrocephalus seems to be a treatable condition.

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Ultrastructure and movement of the ependymal and tracheal cilia in congenitally hydrocephalic WIC-Hyd rats

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Abstract. The aim of the present investigation is to determine whether or not hydrocephalus occurring in hydrocephalic Wistar-Imamichi strain rats (WIC-Hyd) is caused by functional and structural disorders of ependymal cilia. Ultrastructures and movement of cilia in the ependyma of the lateral, III and IV ventricles and aqueduct of Sylvius and in the trachea walls of the animals were examined by means of scanning electron microscopy (SEM), transmission electron microscopy (TEM), and light microscopy using a phase-contrast microscope equipped with a high-speed video recording system. SEM revealed that a marked decrease in the length and number of cilia in the ependymal and tracheal walls occurred in affected male WIC-Hyd. This finding was noted even before the development of ventricular dilatation and was not related to the degree of ventricular enlargement after development of hydrocephalus. A moderate decrease in length and number of cilia was also seen among the normal ciliary tufts in affected female rats which developed a mild degree of hydrocephalus. TEM cilia findings included abnormal axonemal structures such as a lack of dynein arms and displacement of microtubules. The incidence of these ultrastructural abnormalities was found to be greater in affected male rats than in affected female rats. All cilia in affected male rats before and after development of hydrocephalus were immotile. A variety of movement disorders such as immobile, rotatory, and vibratory cilia were observed beside normally beating cilia (motile cilia) in affected female rats which never developed hydrocephalus as severe as that seen in affected male rats. These results seem to indicate that there is a correlation between cilia movement disorder and the degree of ultrastructural abnormalities. Consequently, hydrocephalus developing in affected male and female WIC-Hyd appears to be caused by a motility disorder of ependymal cilia which is part of the primary ciliary dyskinesia (PCD) affecting these animals. The present study appears to indicate that the movement of ependymal cilia may play a role in cerebrospinal fluid circulation, and that dysfunction of ependymal ciliary movement may contribute to development of hydrocephalus in WIC-Hyd rats.

Key words: Ependymal cilia – Congenitally hydrocephalic rat – Situs inversus viscerum – Kartagener syndrome – Immotile cilia syndrome – Primary ciliary dyskinesia

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We have reported [25, 26] that WIC-Hyd rats found in the Wistar-Imamichi strain rat breeding colony at the Research and Development Division of Chugai Pharmaceutical Co., Ltd., Tokyo, are affected by a high incidence of congenital hydrocephalus. A difference between males and females in the severity of hydrocephalus was noted, that is, approximetely 34.9% of the females developed slowly progressive and/or arrested hydrocephalus, although enlargement of the head was not conspicuous. Regardless of this disease condition, they grew up to maturity and became capable of reproduction, and they seldom died of hydrocephalus. On the other hand, approximately 33.7% of the males were affected by rapidly progressive hydrocephalus where there was manifestation of ventricular dilatation resulting in dome-shaped enlargement of the head as early as 1 week after birth, and all of the animals died of raised intracranial pressure (ICP) due to triventricular hydrocephalus caused by secondary stenosis of the aqueduct of Sylvius within 1 month after birth. We suggested that breeding data indicated hydrocephalus in WIC-Hyd rats was communicating, heritable, and X-linked [25]. Also noteworthy was that approximately one-half of the males with hydrocephalus were found to have total situs inversus viscerum, while neither female rats with nor those without hydrocephalus ever developed such a visceral abnormality. Since situs inversus viscerum is known to be closely related to Kartagener

syndrome (KS), we speculated that WIC-Hyd rats might be KS animals.

Regarding KS in human, in 1903 Siewert [44] reported a case complicated by bronchiectasis and situs inversus viscerum. During the period 1933–35, Kartagener [21, 22] demonstrated that bronchiectasis, situs inversus viscerum, and chronic sinusitis were frequently mutually complicated. This disease condition came to be known as Kartagener syndrome. In 1977, Eliasson et al. [14] reported a series of cases in which the syndrome was complicated by male sterility and chronic respiratory infection and proposed that the syndrome might be caused by a lack of or reduction in flagellar and ciliary motility. They called this disease condition "immotile cilia syndrome" (ICS) [14]. In 1981, Sleigh et al. [47] proposed the designation "primary ciliary dyskinesia" (PCD), and then KS and ICS became known as subgroups of PCD because not only ciliary immotility but also various types of ciliary dysfunction [35, 38, 40, 52] were found in bronchial cilia and flagella in KS and ICS. PCD is now considered a systemic ciliary dyskinetic disease. On the basis of the facts, we also speculated that WIC-Hyd rats might have ciliary diskinesia in the trachea and the cerebral ventricle, and would serve as a good animal model for specific PCD hereditary diseases.

In 1943, Olsen [32] described 11 out of 85 patients with dextrocardia (but not KS) to have other defects that included congenital heart disease, hydrocephalus, imperforate anus, cleft palate, and others. To date, six patients with hydrocephalus in association with PCD have been reported [4, 13, 18, 20], but no one has proved an etiological correlation between induction of hydrocephalus and PCD of ependymal cells. In the present study we investigated whether or not WIC-Hyd rats are affected by ciliary dyskinesia in terms of the pathogenesis of hydrocephalus. This was accomplished by means of scanning and transmission electron microscopy (SEM and TEM) and ciliary observation under a phase-contrast microscope utilizing a high-speed videographic technique.

Materials and methods

WIC-Hyd rats were used: 14 normal male rats without hydrocephalus aged from 3 days to 1 month; 11 normal female rats without hydrocephalus aged from 3 to 12 months; 12 female rats with mild hydrocephalus aged from 3 to 12 months; and 19 male rats, aged from 3 days to 1 month with severe hydrocephalus and/or normal ventricular size associated with situs inversus viscerum, the latter category of which it was presumed would develop hydrocephalus if allowed to survive.

Scanning electron microscopy of ependymal and tracheal cilia

Brains and tracheae isolated, respectively, from 6 males and 6 females without hydrocephalus, 7 females with mild hydrocephalus, and 8 males with severe hydrocephalus with or without ventricular dilatation but with situs inversus viscerum, were fixed in 2.5% glutaraldehyde solution for 2 h. Tissue slabs dissected from anatomically designated portions, including the lateral and medial walls of the frontal horn of the lateral ventricle, the walls of the III ventricle, the aqueduct of Sylvius, the floor and roof of the IV ventricle, and the anterior and posterior walls of the middle portion of the trachea, were then washed in cold 0.15 *M* phosphate buffer and postfixed in 2% osmium tetroxide. Because of known regional differences in ependymal configuration, the sample materials studied as described above were taken from similar locations in all instances. After osmium fixation, all specimens were again washed in cold 0.15 *M* phosphate buffer and dehydrated in ethanol, critical point-dried with amyl acetate, coated with gold-palladium, and viewed with a Jeol JSM-800 SEM.

Transmission electron microscopy of ependymal and tracheal cilia

For TEM, samples from each ventricular and tracheal wall adjacent to those used for SEM specimens were prepared. The tissue slabs were fixed, postfixed, and dehydrated in the same fashion as SEM specimens, and were then treated with propylene oxide and embedded in epoxy resin. Ultrathin sections were prepared with an LKB 8800 microtome, stained with lead citrate and uranyl acetate, and examined with a Jeol JEM-100C TEM.

Phase-contrast microscopy of movement of ependymal and tracheal cilia

The animals used for this investigation were 11 males, including those with severe hydrocephalus and others with normal ventricular size but having situs inversus viscerum, 8 males without hydrocephalus, and 5 females with or without mild hydrocephalus. The brain and trachea were removed immediately after decapitation and immersed in Hank's solution at room temperature. The upper and inner walls of the frontal horn of the lateral ventricle, the lateral wall of the III ventricle, the aqueduct of Sylvius, the floor and roof of the IV ventricle, and the anterior and posterior walls of the middle portion of the trachea were exposed under an Olympus dissecting microscope with sufficient care to avoid touching ciliated surfaces with instruments. Small pieces of the ependyma and epithelium were excised with very sharp curved corneal scissors held parallel to the ependymal or epithelial surface in order to obtain a specimen with a thin edge. The ependymal wall surfaces of these specimens were placed tangential to the base of a Petri dish filled with Hank's solution. Movements of the cilia were examined by means of a Nikon phase contrast microscope at ×400 magnification and were recorded on VHS videotape with a Nac MHS-200 high-speed videogram. The frequency and mode of the ciliary beats were assessed by analyzing the recorded videotapes. The mean time lapse between removal of the examination materials and initiation of recording was about 10 min. Ciliary motility can proceed for as long as 3 h after removal of specimens from an animal, but observation was carried out for an average period of 1 h.

Results

Scanning electron microscopy of ependymal and tracheal cilia

In unaffected male and female rats without hydrocephalus (Fig. 1 A), the ependymal surface on the frontal horn of the lateral ventricle was covered with regularly spaced tufts of cilia. Each of the tufts consisted of 20–40 cilia, each 4–6 μm in length and 0.2–0.3 μm in diameter, and fixed in the same direction (Fig. 2 A). Cilia on the walls of the III and IV ventricles and the aqueduct of Sylvius were similarly fixed in one direction. Tracheal

cilia existed among goblet cells, forming thick clusters. In the affected female rats with mild hydrocephalus (Fig. 1 B), the most prominent changes were observed in the ependymal and tracheal cilia. They were shortened and fewer in number, and directional abnormalities, with some cilia extending to full length and other cilia forming clumped clusters, were observed among the normal ciliated tufts (Fig. 2 B). In all samples, the greater part of normal cilia were replaced by abnormal cilia, and these abnormalities were more prominent in the affected male rats with situs inversus viscerum which had not yet developed ventricular dilatation (Fig. 2 C). Identical findings after the development of ventricular dilatation (Fig. 1 C), and similar abnormalities in the III and IV ventricles, the aqueduct of Sylvius, and the trachea also were observed.

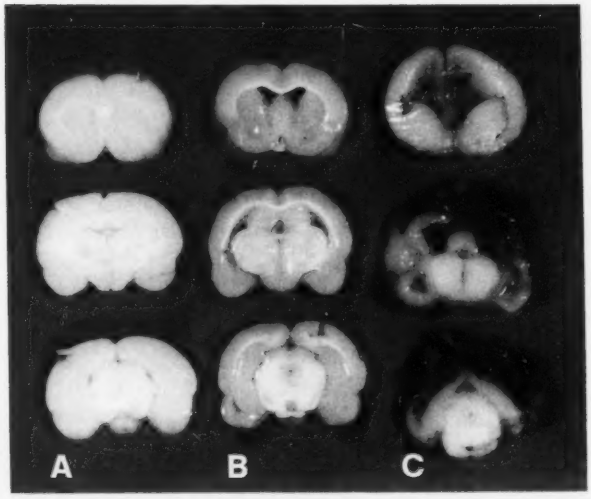


Fig. 1 A–C. Coronal rat brain sections at the anterior horn (*upper*), body (*middle*), and posterior horn (*lower*) levels of the lateral ventricle of (**A**) a 24-day-old unaffected male rat and (**B**) a 12-month-old affected female rat with mild ventricular dilatation. **C** Similar sections of a 24-day-old affected male rat with hydrocephalus show marked ventricular dilatation with intraventricular hemorrhage and subdural hematoma

Transmission electron microscopy of ependymal and tracheal cilia

Shown at left in Fig. 3 is a cross-section of ependymal cilia on the lateral wall of the frontal horn in the lateral ventricle of a 3-day-old normal male rat without hydrocephalus where no axonemal abnormality was found in any structures, including inner and outer dynein arms, spokes, and microtubular alignment. In contrast, an axoneme of the ependymal cilia in a similar region in a 3-day-old affected male rat with total situs inversus viscerum, which had not yet developed ventricular dilatation, was found already to be abnormal, as shown at right in Fig. 3, indicating such various structural abnormalities as the absences of (1) inner and outer dynein arms, (2) peripheral linkages, and (3) central complex, and abnormal microtubular alignment. Similar findings were apparent in affected male rats already hydrocephalic. These findings also were noted in the III and IV ventricles, the aqueduct of Sylvius, and the trachea. Such abnormal cilia also were observed in affected female rats with mild hydrocephalus, but the incidence of ciliary structure abnor-

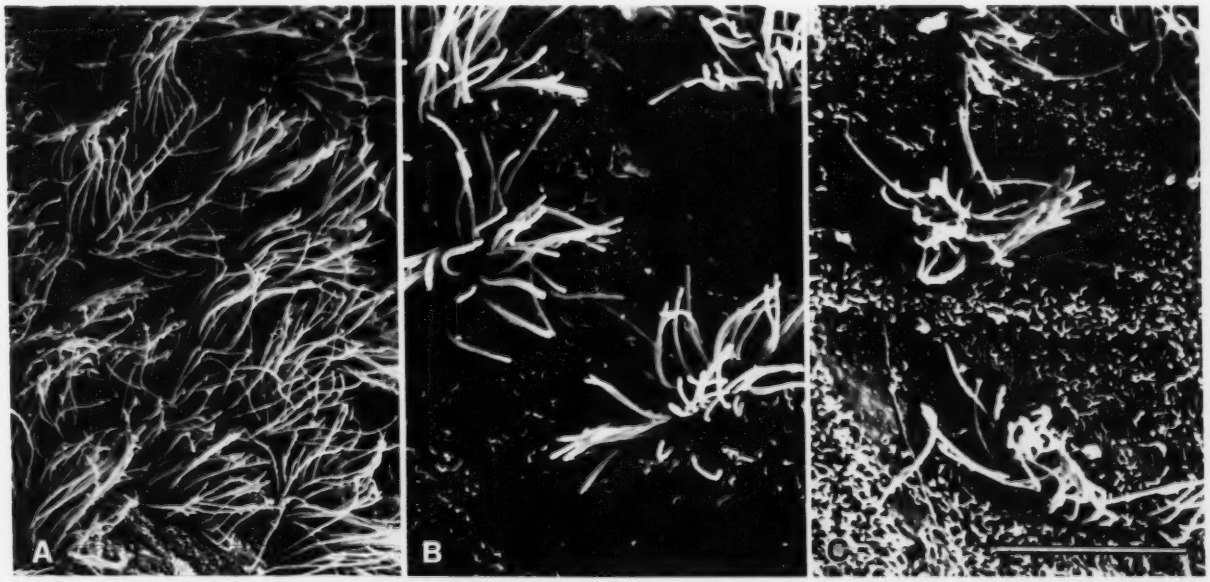


Fig. 2 A–C. Scanning electron micrographs of ciliary processes of upper ependymal wall of lateral ventricle frontal horn depict (**A**) normal ciliary appearance in a 3-day-old unaffected male rat, (**B**) shortened and decreased cilia in a 3-month-old affected female rat with mild hydrocephalic dilatation, and (**C**) markedly decreased and randomly oriented cilia in a 3-day-old affected male rat with situs inversus viscerum which has not yet developed hydrocephalus. *Bar* = 10 μm

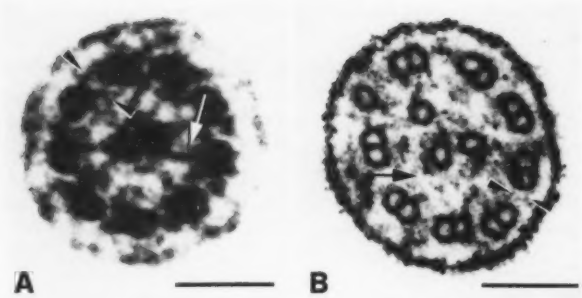


Fig. 3A, B. Transmission electron micrographs of horizontal cross-sections of cilia, depicting (**A**) normal axonemal structures such as inner and outer dynein arms (*arrowheads*) and radial spokes (*arrow*) in a 3-day-old unaffected male rat and (**B**) the lack of both dynein arms (*arrowheads*), displacement of the peripheral tubules and the lack of radial spokes (*arrow*) in a 3-day-old affected male rat with situs inversus viscerum which has not yet developed hydrocephalus. *Bar* = 0.1 μm

malities was less than in the case of affected males with/without hydrocephalus.

Phase-contrast microscopy of movement of ependymal and tracheal cilia

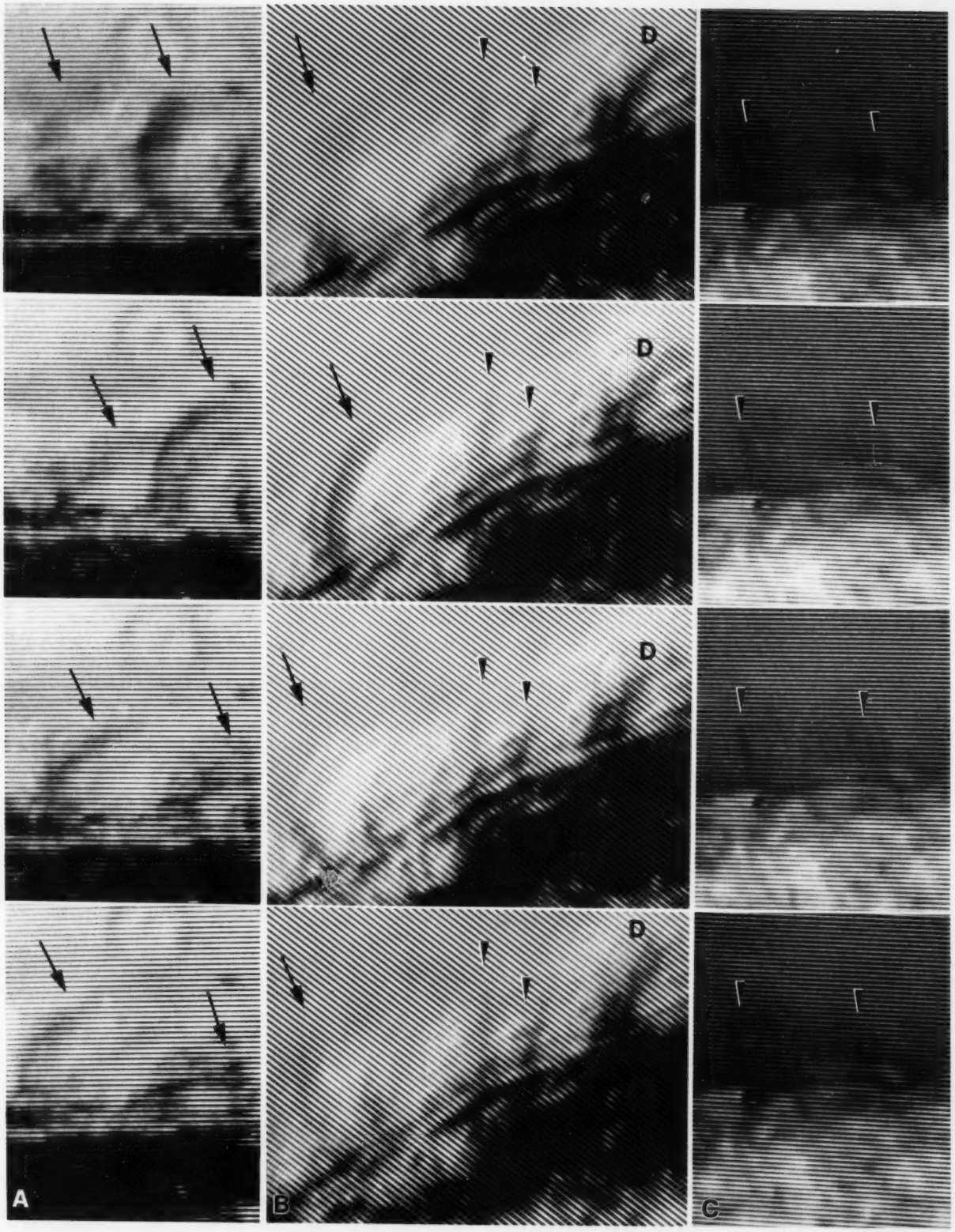
High-speed-videotaped static images of the movement of ependymal cilia on the frontal horn of lateral ventricle are shown in Fig. 4. Each cilium in an unaffected male rat without hydrocephalus (Fig. 4A) beat with a rapid and uniform motion. In other unaffected male and female rats without hydrocephalus, cilia of the lateral, III and IV ventricles, the aqueduct of Sylvius, and the trachea showed a metachronal movement and beat with a frequency of 1000–2000 cycles per minute. In the hydrocephalic female rat (Fig. 4B), the ciliary movement was characterized by various patterns, including normal to-and-fro movement, vibratory and rotatory motion, and akinesia; that is, the synchronized to-and-fro movement of the cilia in a certain direction observed in unaffected rats without hydrocephalus was completely perturbed by the mosaic distribution of ciliary tufts and different modes of movement, and the number of cells with motile cilia was lower than in normal subjects. Similar findings were observed on the walls of the III and IV ventricles, the aqueduct of Sylvius, and the trachea in other affected female rats with hydrocephalus. Affected male rats with situs inversus viscerum which had not yet developed ventricular dilatation already demonstrated immotile cilia (Fig. 4C). In other hydrocephalic males, none of the ependymal and tracheal cilia were found to show any beat, regardless of ventricular size.

Discussion

The results obtained in the present study demonstrated that affected male WIC-Hyd rats with situs inversus viscerum, before and after development of ventricular dilatation, have immotile cilia in the ventricular ependyma and trachea, leading to the assumption that abnormality in the axonemal structure of cilia might have a role in the pathogenesis of ciliary motility disorder. Contrarily, affected female WIC-Hyd rats with mild hydrocephalus were found to have a lesser degree of axonemal structural abnormality and to display a mosaic mode in ciliary movement due to the irregular distribution of kinetic, dyskinetic, and immotile cilia both in ventricular ependyma and trachea. From these observations, one could describe affected male and female rats respectively as modeling human ICS and PCD. There also was a strong suggestion that abnormal axonemal structures of the cilia, such as the absences of dynein arms, radial spokes, and microtubules, might have a role in the pathogenesis of ciliary motility disorder. A potential correlation between morphological changes of the axonemal structure and the functional alterations of ciliary movement in WIC-Hyd rats, as described below, will be discussed.

Although there have been many reports in regard to SEM images of ependymal cilia in experimental hydrocephalus induced by various methods, including intraperitoneal viral infection, intrathecal bacterial infection, or intracisternal injection of kaolin or silicone oil [17, 31, 33, 55], only a few reports have been published in regard to SEM investigation of ventricular cilia in animals with congenital hydrocephalus [9, 23]. In the assessment of SEM images of the lateral ventricular wall in rats with hereditary hydrocephalus, Lindberg et al. [27] noted that the cilia were shortened, fewer in number, and clumped or matted. Using SEM, Bannister and Mundy studied ependymal surfaces of the ventricles of two congenitally hydrocephalic Hy-3 mice in comparison with that of an infant with hydrocephalus complicated by meningocele and Chiari malformation. In the basal regions of the lateral ventricles of the Hy-3 mice, the ependymal wall possessed normal cilia, but the upper ventricular wall was found to be devoid of cilia, whereas no abnormal change in ependymal cilia in the lateral ventricle of the infant was noted [7]. They concluded that the changes in the ventricular wall and the coarse ependymal cilia could be attributed to thinning of the ventricular wall resulting from increased ICP due to hydrocephalus, and were not the cause but the result of hydrocephalus. By contrast, Afzelius [4] described the defective cilia as being the primary cause of hydrocephalus and the high intraventricular pressure as its consequence. In the affected male rats with situs inversus viscerum in this study, the changes in ependymal surfaces, where the ependymal

Fig. 4A–C. Four frames of a videogram show (*top* to *bottom*) successive changes at 0.005-s intervals in (**A**) a 3-day-old unaffected male rat (*arrows* in each frame indicate ciliary beat), (**B**) various kinds of cilia such as immotile (*arrowheads*), dyskinetic (*D*) and beating cilia (*arrows*) in a 3-month-old affected female rat with mild hydrocephalus, and (**C**) ependymal cilia, all immotile (*arrowheads*) in a 3-day-old affected male rat with situs inversus viscerum which has not yet developed hydrocephalus. Magnification ×8000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cilia were coarse, shortened, and with thin diameters, and/or clustered or entangled in multiple directions, were found prior to ventricular enlargement. These findings would suggest that morphological changes of the cilia are not due to increased intraventricular pressure or stretching of the ependymal walls secondary to ventricular enlargement, but rather than they are a potential cause of hydrocephalus.

The relationship between axonemal structure and the movement of cilia and flagella has been studied in investigations using cytozoons, sea urchins, and tetrahymenae [2, 16, 19, 29, 51]. Many reports have been published in regard to correlation between the ultrastructure and the motility of the tracheal cilia and the spermal flagella in human cases [3, 4, 14, 35, 36, 47]. The first step in unraveling ICS was the discovery by Pedersen and Rebbe [36] of a case of immotile spermatozoa devoid of the dynein arms. Afzelius studied four subjects who produced immotile sperm, three of whom had frequent episodes of bronchitis and sinusitis where there was no mucociliary transport. He found that cilia from cells of these patients lacked dynein arms [3]. These studies strongly suggested that the absence of dynein arms was the cause of immotility of spermatozoa and cilia. In addition to the complete absence of both dynein arms, defects of the inner or outer dynein arms, spoke heads, one or both microtubules, and the central sheath also have been implicated as axonemal abnormalities of sperm and cilia in cases of motility disorder [5, 49, 50, 54]. Following these observations, the mechanism of ciliary or flagellar beats was investigated by various scientists and found to be based on the sliding and/or switching of doublet tubules by dynein arms (ATPase) [15, 42, 43], and it also was shown that the cyclic-AMP-dependent proteinase and the regulatory proteins constituting ciliary substance intermediately work to create the coordinate and metachronal movement of cilia and flagella [41, 45, 46].

With regard to hydrocephalus and ependymal ciliary dyskinesia, Bryan studied mice homozygous for a recessive, pleiotropic, mutation hydrocephalic-polydactyly (hpy) and found that the male hpy mouse was affected by postnatal hydrocephalus and complete sterility and that the female hpy had reduced reproductive performance. He suggested that the fertility problems and the development of hydrocephalus could have arisen as consequences of defective flagella and ciliary axonemes of oviduct and ependyma [10].

A small number of patients in whom hydrocephalus was associated with PCD have been reported to date [4, 13, 18, 20, 32]. The reason for the small number reported is probably due in part to the low incidence of PCD, to the lack of recognition of the possibility that PCD may be associated with mild hydrocephalus, and to insufficient medical examination. Following his assessment in 1943 of 85 patients with congenital dextrocardia, Olsen [32] mentioned that 11 of them had other defects including hydrocephalus, and that 16.5% (14/85) of them had bronchiectasis. Afzelius [4] examined the brains of seven patients with ICS by CT. In three of these patients, the ventricular system and sulci were slightly enlarged. Greenstone et al. [18] reported a 12-year-old boy with PCD and bronchiectasis who had developed hydrocephalus in the neonatal period. They mentioned that the concurrence of hydrocephalus and PCD was of interest, because it might suggest a function of cilia in the embryonic development of CSF pathways. Jabourian et al. [20] observed a 15-year-old girl with KS, an immotile ciliary disorder consisting of sinusitis, bronchiectasis, and situs inversus viscerum, who developed persistent headaches and was found to have communicating hydrocephalus with evidence of impairment of CSF circulation at the level of the tentorium. This patient required a ventriculoperitoneal shunt, after which there was relief of the hydrocephalus and its associated symptoms. These authors assumed that ependymal cilia normally kept the aqueduct patent and that the risk of stenosis was increased in patients with ciliary immotility. De Santi et al. [13] reported a particular form of PCD (ciliary aplasia) in a girl with bronchiectasis who developed hydrocephalus in the neonatal period. CT showed triventricular hydrocephalus caused by aqueductal stenosis, then a ventriculoatrial shunt was inserted and her subsequent neurological development was normal. De Santi et al. suggested that ependymal ciliary defects in PCD might be a contributory embryological factor in the pathogenesis of particular forms of hydrocephalus, and that there might be a causal relation between PCD and hydrocephalus. These previous investigations by various scientists lend support to our speculation that abnormal fine structures of ependymal and tracheal cilia may be intimately related to ciliary motility disorder and hydrocephalus.

Purkinje [37] was the first scientist to observe the movement of cilia on the walls of cerebral ventricles in full-term sheep fetuses, and he found that the cilia were long and pointed and vibrated in a whip-like fashion. To date, there have been several reports on the relation between the beat of cilia and CSF currents on the ventricular surface [1, 11, 12, 30, 39, 48, 53, 56, 57]. Konno and Shiotani [24], utilizing a phase-contrast microscope, reported that the red blood corpuscles moved toward the foramen of Monro in the lateral ventricle of 2- to 8-week-old dogs. Worthington and Cathcart [11, 56, 57] observed the beating cilia in surviving ependyma of adult human brains and then mapped the ciliary currents in each of the ventricles. They concluded that the function of cilia in the central nervous system is to maintain the CSF in constant motion and to clear cellular debris from the ependymal surface of the ventricular system. Milhorat [28] proposed that the strong cilia-induced currents near the ventricular walls are important for intraventricular CSF circulation, but others [6, 39, 52] attributed only a minor role to the cilia, and some [34] regard them as nonfunctional rudimentary structures. Utilizing SEM, Yamadori and Nara [58, 59] observed in adult mice the directions of ciliary beat on the walls of the whole brain ventricular system, including the central canal, and revealed that the pattern of directions of the ciliary beat was always the same in each individual in the series despite different positions at the time of fixation, and the pattern was in agreement with the anticipated flow of the fluid. Yamadori then concluded that the ciliary movement has a close relationship with the CSF current and must be an important

factor in producing and regulating the flow of CSF within the ventricular system.

The facts established by the aforementioned investigators allow us to hypothesize that the flow of the CSF might be variously restricted by impairment of ciliary movement, especially at the aqueduct of Sylvius, which is an extremely narrow canal for the passage of CSF, leading to the development of hydrocephalus. Hence, marked CSF stagnation due to ICS might produce high intraventricular pressure and generate enlargement of the lateral and III ventricles in hydrocephalic males, while slight CSF stagnation owing to ciliary dyskinesia might result in mild ventricular dilatation in hydrocephalic females. Although the pressure gradient between CSF formation and absorption, the pressure variations associated with arterial pulse and respiration, and the continuous outpouring of new CSF are thought to be important factors when considering the hydrodynamics of the ventricular system [8, 28, 39], our findings clearly show that the movement of ependymal cilia may also play an important role in CSF flow and that the dysfunction of ependymal ciliary movement may contribute to the ventricular dilatation associated with hydrocephalus in cases of PCD.

Noteworthy in the present experimental model are the findings that hydrocephalic males demonstrated progressive hydrocephalus which might belong in the ICS category, and that hydrocephalic females demonstrated slowly progressive and/or arrested hydrocephalus which might pertain to the PCD genre. It is believed the present model could well serve as a good way of studying the pathogenesis of PCD. Further studies on the distribution, activity, and function of human and animal ependymal cilia, as well as the relations between ciliary motility and CSF dynamics, also are warranted.

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Correlation of ventricular size and head circumference after severe intra-periventricular haemorrhage in preterm infants

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Abstract. No detailed information is available about the timing and correlation of objectively gauged ventricular width (VW) and the rate of growth of the occipitofrontal circumference in premature infants with intraventricular haemorrhage preceding progressive ventricular dilation. For this study, two groups were selected according to clinical course: group A ($n=6$) had ventriculomegaly with no signs of raised intracranial pressure, while patients in group B ($n=7$) developed progressive ventricular dilation after a period of latency. A VW between 0.9 and 1.4 cm (group A) did not affect normal head growth, whereas a VW greater than 1.5 cm was always associated with the development of hydrocephalus. Our data further suggest that the widely used criterion of a head growth rate of more than 2 cm/week is a relatively poor criterion for the definition of post-haemorrhagic hydrocephalus.

Key words: Preterm infants – Intraventricular haemorrhage – Ventricular width – Occiptofrontal circumference – Post-haemorrhagic hydrocephalus – Ventriculomegaly

Intra-/periventricular haemorrhage (IVH/PVH) is the most common and serious neurological disorder in premature infants of less than 35 weeks' gestation. Post-haemorrhage ventricular dilation is a well-known complication and its evolution and course depend on the severity of the initial IVH/PVH. Fifty-five percent of the survivors of severe IVH with periventricular involvement will develop progressive ventricular dilation [13].

For differentiation between progressive ventricular dilation, i.e. post-haemorrhagic hydrocephalus (PHH), and ventriculomegaly (VM), the increase in occipitofrontal head circumference is used as an important determinant. However, to date no detailed information has been available about the timing and correlation of objectively gauged ventricular size and the rate of growth of head circumference.

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The aims of this study were to determine the critical ventricular size above which a pathological rate of head growth occurs and to estimate the maximum degree of ventricular dilatation that does not induce pathological head growth. Thirdly, we asked whether there is development of hydrocephalus in any patients without a head growth rate of 2 cm/week or more.

Patients and methods

From March 1986 to January 1988 50 neonates with an intraventricular haemorrhage (IVH) were admitted to the neonatal intensive care unit. Thirty-two had an IVH grade 3 and 18 were suffering from an IVH grade 3 plus periventricular haemorrhage (PVH). The grading of IVH was according to the classification of J. J. Volpe [13]. Twenty-eight patients died (56%), 10 developed PHH (20%), and 12 showed remission (24%) The selection criteria for this study were: IVH grade 3 or IVH plus PVH and dilation exceeding 0.5 cm of at least one lateral ventricle.

Of the 22 patients who survived the acute episode of haemorrhage, 13 met the criteria for entry into this study. Three patients with PHH (1 patient had excessive leukencephalomacia that did not allow accurate measurement of the lateral ventricles; 1 patient underwent surgical evacuation of the blood clot; 1 patient already had hydrocephalus on admission) and 6 patients who showed remission (3 were transferred and therefore did not undergo control measurements; 3 never reached a ventricular width of 0.5 cm) had to be excluded.

The 13 infants who met the entry criteria were divided into two groups. Group A consisted of 6 infants who either showed a spontaneous remission after an initial delay (2 patients) or developed a persistant VM (4 patients), while 7 infants who developed PHH formed group B.

Hydrocephalus was defined as dilation of at least one lateral ventricle, with a ventricular width of 1.5 cm or more, in addition to a pathological increase of occipitofrontal circumference of more than 1 cm/week [4, 7, 11].

Ventriculomegaly was defined as a ventricular width above 0.5 cm without pathological increase of occipitofrontal circumference or clinical signs of raised intracranial pressure (ICP). Ventricular width was defined as the widest measurement taken perpendicular to the longest axis of the coronal section of the lateral ventricle in a plane which included the III ventricle just behind the foramina of Monro [10]. Measurement were taken at least once weekly using a real-time-sector scan (ATL Mark 600, 5 and 7.5 MHz). Measure-

ment of the occipitofrontal circumference was done weekly as well, using the percentiles for head circumference from the Hammersmith Hospital, London [3].

Trans-fontanelle measurement of ICP (LADD Monitor) was performed only if clinical signs of raised ICP were apparent. All patients except two received acetazolamide (50 mg/kg day) [8, 9, 12]. All measurements took place before the start of any invasive diagnostic intervention or therapy (e.g. lumbar puncture, ventricular puncture, external drainage or shunt implantation) that would reduce the volume of cerebrospinal fluid.

Group A

The median gestational age of these 6 patients was 31 weeks (range: 29–33 weeks). The median birth weight was 1370 g (1010–2030 g). The haemorrhage occurred after a median life period of 5.5 days (5–9 days). The median observation period was 10 weeks (7–22 weeks). The median maximum ventricular diameter (either right or left) was 0.8 cm (0.6–1.4 cm; Table 1). The patients reached the point of maximum ventricular dilation after a median period of 22.5 days (7–37 days). In none of the patients did the dilation of one lateral ventricle exceed 1.5 cm. The median lateral diameters during the whole period of observation ($n=59$ measurements) were: right 0.8 cm (0.1–1.4 cm), left 0.8 cm (0.2–1.3 cm). In this period the median increase in occipitofrontal circumference was 0.6 cm/week (0–1.5 cm/week). The median maximum head growth was 1.2 cm/week (1.0–1.5 cm/week). None of the patients in this group had an occipitofrontal circumference exceeding the 50th percentile. None of the patients showed clinical signs of raised ICP.

Group B

The median gestational age in this group was 32 weeks (29–38 weeks). The median birth weight was 1730 g (1160–3200 g). The haemorrhage occurred after a median life period of 3 days (1–8 days). If diagnostic or therapeutic procedures that would result in a reduction of the volume of cerebrospinal fluid were necessary, observation for the purposes of this study was terminated.

We divided the observation period in two parts and called these period 1 (B_{P1}) and period 2 (B_{P2}). B_{P1} covered the time between onset of haemorrhage and reaching a ventricular dilation of 1.5 cm, while B_{P2} was the period between the point at which a ventricular diameter of 1.5 cm was exceeded and invasive intervention started.

Table 1. Ventricular width, maximum ventricular width, occipitofrontal circumference and maximum occipitofrontal circumference groups A and B (median and range). VW, Ventricular width; OFC, occipitofrontal circumference

	Group A ($n=6$)	Group B ($n=7$)	
		Period 1	Period 2
Median VW (cm): right	0.8 (0.1–1.4)	<1.5	2 (1.3–3.6)
left	0.8 (0.2–1.3)	<1.5	1.85 (1.5–2.5)
Median maximum VW (cm)	0.8 (0.6–1.4)		2.2 (1.7–3.6)
Median OFC (cm/week)	0.6 (0 –1.5)	0.6 (0.3–1.5)	1.6 (0.1–2.4)
Median maximum OFC (cm/week)	1.2 (1.0–1.5)	0.8 (0.4–1.5)	1.9 (1.6–2.4)

The patients reached the point of dilation of at least one lateral ventricle of 1.5 cm after a median duration of 17 days (10–40 days). In this period of ventricular dilation, the median of occipitofrontal circumference was 0.6 cm/week (0.3–1.5 cm/week). The median maximum growth rate of the occipitofrontal circumference was 0.8 cm/week (0.4–1.5 cm/week). In this period no clinical signs of raised ICP were observed.

Results

After a ventricular width of 1.5 cm was exceeded the median increase in occipitofrontal circumference was 1.6 cm/week (0.1–2.4 cm/week). There was a highly significant difference between the two periods ($P<0.0005$!, Wilcoxon rank sum test). The median maximum rate of growth of the occipitofrontal circumference was 1.9 cm/week (1.6–2.4 cm/week), showing a significant difference in comparison to B_{P1} ($P<0.001$) and to group A ($P<0.0025$). Furthermore, there was a significant difference between the median increase in occipitofrontal circumference in group B_{P2} and the maximum median increase in occipifrontal circumference in group A ($P<0.025$, Wilcoxon rank sum test). The median duration of observation in period 2 in group B was 3 weeks (1–6 weeks).

A ventricular width exceeding 1.5 cm was in all cases followed by a pathological rate of growth of the occipitofrontal circumference in the following 7 days (Fig. 1). In all but two patients it was also the maximum growth rate. Only 2 of 7 patients with PHH had an occipitofrontal circumference above the 90th percentile.

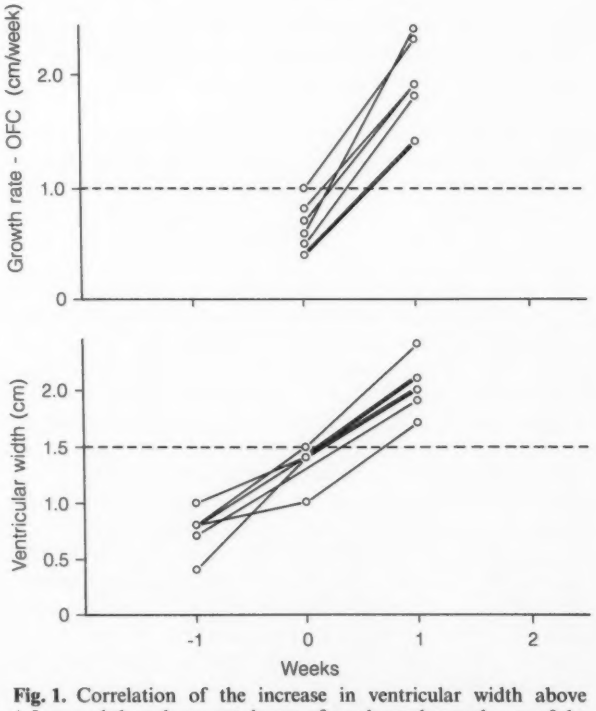

Fig. 1. Correlation of the increase in ventricular width above 1.5 cm and the subsequent degree of accelerated growth rate of the occipitofrontal circumference (OFC) in group B

During this period we observed clinical signs of raised ICP in 4 patients. These signs were confirmed in all cases by raised values for measurements of ICP using the Ladd monitor.

The median ventricular diameters were: right 2.0 cm (1.3–3.6 cm), left 1.85 cm (1.5–2.5 cm). There was no significant difference between patients who received acetazolamide medication and those who did not. All patients in group B underwent shunt implantation in the long run.

Discussion

An essential criterion for the diagnosis of hydrocephalus following IVH/PVH is the occurrence of ventricular dilation of a certain degree associated with a pathological increase in head circumference and at least the clinical features of raised ICP. One of the most difficult differentiations is that between rapidly progressive ventricular dilation and the slowly progressive ventricular dilation that usually indicates cessation of dilation [13]. Both types of posthaemorrhagic dilation are associated with a clinically asymptomatic period of varying duration. Hill and Volpe once described this phenomenon as "normal pressure hydrocephalus" [5]. Korobkin stated that this period of asymptomatic progressive ventricular dilation may occur until a critical point is reached after which head circumference expands rapidly, due to the exhaustion of the relatively high compliance mechanisms of immature cerebral tissue [6, 14]. Allan et al. suggested that a ventricular diameter of 1.5 cm might be such a critical point [1]. Our study confirmed this hypothesized "critical point of no return" at a ventricular dilation of 1.5 cm. None of our patients in group A (who did not have ventricular dilation exceeding 1.5 cm) developed PHH, while all patients in group B did.

There were no significant differences between group A and period 1 in group B, which supports the theory of a period of "clincially asymptomatic dilation" preceding the progressive dilation. At this point it was absolutely impossible to differentiate between the two groups. A ventricular diameter exceeding 1.5 cm was always a predictor of the development of PHH.

The question whether an increase in occipitofrontal circumference is pathological or not is quite difficult to answer. Several authors have come to the conclusion that rate of head growth up to 1 cm/week is normal [4, 7, 11]. On the other hand, the important criterion in the diagnosis of hydrocephalus often described in the literature is an increase in occipitofrontal circumference of 2 cm/week or more [1, 2]. Thus, there is a gap between "normal head growth" and the definitely pathological rate of increase in occipitofrontal circumference of 2 cm/week or more. Our data suggest that the values for weekly head growth positioned in this gap could be predictors of subsequent development of PHH [12, 13]. Our studies showed an absolutely normal median increase in occipitofrontal circumference in groups A and B_{P1} (both +0.6 cm/week), in contrast to the significantly different median increase in occipitofrontal circumference of 1.6 cm/week in group B_{P2}. Thus, observing over a long period (mean 3 weeks) in group B_{P2}, we did not see a median head growth of 2 cm/week or more. The median maximal increase in occipitofrontal circumference of 1.9 cm in group B_{P1} came very close to this mark. However, only two patients showed an increase in occipitofrontal circumference of 2 cm/week or more, each only once in the 7 days following the increase of one ventricular diameter beyond 1.5 cm. In fact, all but two patients had their maximal increase in occipitofrontal circumference in that week. Because head growth of 2 cm/week was so rarely seen, we drew the conclusion that an increase in occipitofrontal circumference of 1.5 cm/week should prompt close clinical examination of the patient in order to rule out the possibility of developing hydrocephalus.

Another important observation we would like to draw attention to is that an occipitofrontal circumference crossing the 90th percentile was not always present before the development of PHH: only 2 out of 7 patients with PHH showed this symptom. Finally, we would like to emphasize that ventricular diameter of 1.5 cm was the most reliable criterion for early diagnosis of the development of PHH.

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The widened frontal subarachnoid space

A CT comparative study between macrocephalic, microcephalic, and normocephalic infants and children

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Abstract. The computed tomographic scans of the heads of 67 infants and children with frontal subarachnoid space widening seen during a 5-year period were retrospectively studied. Only 22.3% of patients had macrocephaly. Comparison of the clinical and radiologic characteristics of subarachnoid widening in macrocephalic children and in normocephalic or microcephalic children showed no significant differences. It is concluded that undue emphasis has been laid on the association between this radiologic sign and macrocephaly. Widening of the subarachnoid space in children may be a variation of normal development of brain whereby there is a transient accumulation of cerebrospinal fluid in the frontal region. The term "external hydrocephalus" may therefore be inappropriate in the absence of significant ventricular widening and clinical signs of raised intracranial pressure.

Key words: Macrocephaly – External hydrocephalus – Benign subdural effusion

Since the advent of computed tomography (CT) of the head of infants and children, several diagnoses have been assigned to the enlarged frontal subarachnoid space with a normal or slightly dilated ventricle. The diagnoses in children with macrocephaly and this radiologic finding have been given various names, such as external hydrocephalus [1, 9], benign enlargement of the subarachnoid space [10], benign subdural collection [4, 17], and pseudohydrocephalus-megalocephaly [18]. In one study, children were subjected to craniotomy and shunted [2]. Relatively little attention has been given to the occurrence of a widened subarachnoid space in non-macrocephalic infants and children. The purpose of the present paper was to study the records at this institute of all children with this radiologic finding, irrespective of head size, and make a comparison between the normocephalic children and those with macro- or microcephaly.

Materials and methods

The CT head scans of all infants treated at this institute who showed only a widened frontal or frontotemporal subarachnoid space during the 5-year period from January 1985 to December 1989 constitute the material for this study. Relevant clinical information such as occipitofrontal head circumference, age, sex, and primary diagnosis were extracted from the case notes. The following categories of patients were excluded from the study: trauma cases, children with more than mild ventricular and basal cistern dilatation, and children with cerebral atrophy. The latter group was identified using the criteria of Maytal et al. [9], namely: (1) uniform prominence of the sulci of the entire brain, (2) proportional dilatation of the ventricle with the subarachnoid space, and (3) interhemispheric fissures normal or uniformly widened in their entire course.

All children were scanned under sedation using a deep intramuscular injection of a cocktail of Demerol (meperidine hydrochloride) 2 mg/kg, Phenergan (promethazine hydrochloride) 1 mg/kg and Largactil (chlorpromazine) 1 mg/kg. Most examinations were done without contrast enhancement. The degree of subarachnoid widening was divided into two grades:

Grade I: Subarachnoid widening confined mainly to the frontal region with only an anterior "slit" of the interhemispheric fissure (Fig. 1a).

Grade II: The widening extending to the frontoparietal region with a wide separation at the interhemispheric fissure (Fig. 1b).

The total number of patients was 67, and these were grouped into four categories based on their presenting features and the clinical diagnosis at CT examination of the head, as follows:

Macrocephaly: Children being evaluated for a large head or rapidly increasing head size and who had a maximal occipitofrontal circumference (OFC) greater than the 95th percentile.

Microcephaly: Patients whose maximal OFC was below the 5th percentile, and also those with premature closure of cranial suture.

Meninigits: Patients with proven or suspected meninigits.

Miscellaneous: All remaining patients, with a wide range of clinical indications for CT of the head, such as seizure disorders, failure to thrive, and delayed developmental milestones.

Results

There were 48 male and 19 female patients. The age, sex and distribution of subarachnoid widening in the four

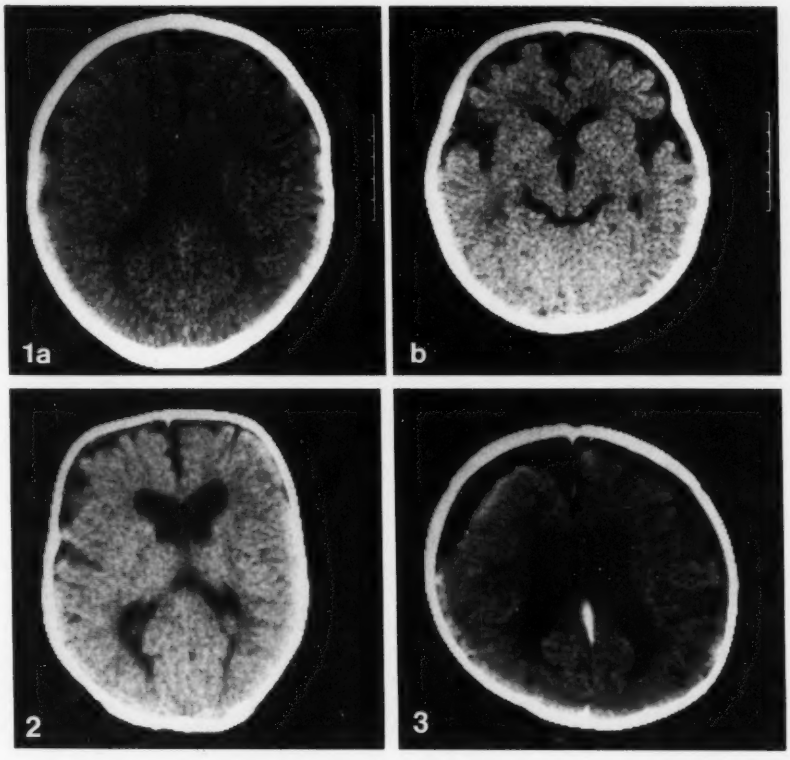

Fig. 1 a, b. Subarachnoid widening. **a** Grade I, **b** Grade II

Fig. 2. Right-sided unifrontal subarachnoid widening in a child with craniosynostosis

Fig. 3. Child with meningitis: "membrane" formation on the anterior aspect of right frontal lobe in a contrast-enhanced CT scan

Table 1. Sex, age and distribution of subarachnoid widening in the four patient categories

Category	Male	Female	Total	Total patients (%)	Age (months)	
					Mean	Range
Macrocephaly	12	3	15	22.3	11	3.5–30
Microcephaly/ craniosynostosis	7	3	10	14.9	6	0 –24
Meningitis	7	2	9	13.4	7.5	4 –12
Miscellaneous	22	11	33	49.2	9	3 –25

Table 2. Grades of subarachnoid widening in the four categories

	Grade I	Grade II
Macrocephaly	7	8
Microcephaly/craniosynostosis	8	2
Meningitis	6	3
Miscellaneous	26	7

categories is summarized in Table 1. Although the macrocephaly group was the single largest group of children, it only accounted for 22.3% of cases. There were no significant differences in age and sex distribution between the various categories. Table 2 shows the distribution of the two grades of subarachnoid widening. Macrocephalic cases were equally distributed between grade I and grade II widening. In the other groups of children, however, there was a preponderance of grade I widening.

Of the four macrocephalic children who had undergone follow-up CT examination, the frontal widening has significantly reduced after 1 year in 3 children. Subarachnoid widening was symmetrical in all macrocephalic patients.

Two of the ten children in the microcephaly group were asphyxiated at birth, whilst a further two had a strong family history of microcephaly. There were three cases of craniosynostosis. One of these showed unilateral subarachnoid widening (Fig. 2), whilst in another the subarachnoid widening resolved after suturectomy. Two of the four children with follow-up examinations showed reduced subarachnoid widening.

Amongst the meningitis group, three children showed a high attenuating membrane around the area of dilated subarachnoid spaces (Fig. 3); only two children showed resolution in 6 months. The associated organisms were *Haemophilus* in five cases, meningococcus in two cases, and there was one case each of tuberculous and aseptic meningitis.

The indications for CT examination in the miscellaneous group included failure to thrive and delayed developmental milestones (13 cases), seizure disorders (12 cases), and focal neurological deficits (8 cases). Four of the six children in this group for whom there were follow-up scans showed reduction of the subarachnoid space width within 1 year.

Discussion

In 1914 Dandy and Blackfan [7] used the term "external hydrocephalus" to describe the association of widened subarachnoid space with raised intracranial pressure. Recently, Robertson and Gomez [16] associated it with widened subarachnoid space and mild to moderate ventricular enlargement, on the basis of CT head findings in children with rapidly enlarging heads. Since then several papers have called attention to the association of bifrontal widening with rapidly enlarging head in infants. Whilst some authors associate this condition with ventricular enlargement [13, 16, 17], others report normal or slightly dilated ventricles [10, 14, 18]. Furthermore, there is no agreement as to the precise location and/or cause of the bifrontal area of low attenuation. In this regard Briner and Bodensteiner [4] and Robertson and associates [17] concluded that the characteristic CT finding of bifrontal low attenuation was due to "benign subdural effusion." On the other hand, Anderson, who carried out craniotomy in four of his patients, concluded that the area of low attenuation was due to deep subarachnoid space – and that it contained only CSF [2]. Modic et al. [11] think that the finding was not specific and that it was not always possible to determine the nature and/or precise location of fluid – subdural or subarachnoid space.

In his definition of external hydrocephalus, Raimondi [15] proposes that in the presence of a pathologic accumulation of CSF, there is free movement of the fluid from the subarachnoid space through the membrane into the subdural space. The implication of this theory is that the fluid in both compartments is CSF and the distribution is determined by the amount of abnormal CSF accumulation.

Concerning the pathogenesis of bifrontal hypodense areas on brain CT in children, several hypotheses have also been put forward. Robertson et al. [17] suggested that the sulci were dilated by CSF whose reabsorption was obstructed by subdural fluid. Barlow [3] concluded from a report of five cases that there might be some anatomic or functional obstruction of various etiologies at the arachnoid villi level, resulting in widened subarachnoid space. Kendall and Holland [8] described it as a mild form of communicating hydrocephalus.

Raimondi [15] defines hydrocephalus simply in terms of a pathological increase in intracranial CSF volume, irrespective of its pressure. He further classifies it into intraparenchymal and extraparenchymal hydrocephalus and feels that the progression from intraparenchymal to extraprenchymal hydrocephalus may correspond with the site of abnormal CSF accumulation. In this regard subarachnoid CSF accumulation is thought to be a stage in a spectrum of stages ranging from intracellular fluid collection to intraventricular and subarachnoid CSF collection. Raimondi further pointed out that in this early stage of hydrocephalus the subarachnoid space widening may not be associated with dilated ventricles.

Mori [12], on the other hand, feels that the diagnosis of hydrocephalus should be restricted to situations where there is increased retention of CSF in association with increased pressure and ventricular enlargement.

Despite the various hypotheses as to the pathogenesis of bifrontal subarachnoid widening in children, all authors seem to agree that this finding is of a benign and self-limiting nature, and does not require any surgical intervention. We are still in the dark as to the factors that reverse or stabilize the accumulation of CSF/subdural fluid. None of the proponents of subdural effusion as a cause of widening have put forward any precise etiologic factor.

Due to the design of this study, a radiologic study of widened subarachnoid spaces was carried out in a group of children irrespective of whether they had macrocephaly or not. This is in contrast with the majority of previous reports, which have focused on children with an enlarging head. Our results show no significant differences in clinical and radiologic characteristics between children with macrocephaly and those who were normocephalic or microcephalic. Furthermore, less than 25% of children with a widened frontal subarachnoid space had macrocephaly, which disagrees with impressions previously created that this phenomenon was invariably associated with a large head. It has been suggested that non-macrocephalic children with subarachnoid widening should be regarded as suffering from cerebral atrophy [5, 8, 11]. Radiographic criteria have, however, been developed in an attempt to differentiate benign widening of hydrocephalus subarachnoid space from cerebral atrophy [9]. Despite the exclusion of cerebral atrophy cases in this study, using the above criteria, there were still nonmacrocephalic children with this finding.

The significance of bifrontal subarachnoid widening in children with craniosynostosis in the absence of significant ventricular dilatation is not certain. Although Maytal et al. [9] claim that the presence of this finding in craniosynostotic children was diagnostic of cerebral atrophy, Collman et al. [6], in a review of hydrocephalus in craniosynostosis, found that dilated subarachnoid space was not a good indicator of intracranial pressure.

The subarachnoid widening in cases of meningitis was different from that in the other categories of patients only in that a meningeal "membrane" was present. It is therefore probably unrelated to meningitis. Although relatively few patients had follow-up scans, the pattern of regression of widening shown was similar in all groups of patients.

On the basis of the findings of this study, it is suggested that subarachnoid space widening in children may be a variation in the process of normal development of the brain whereby there is a transient accumulation of CSF in the frontoparietal region. Children with rapidly increasing head size may therefore have an accentuation of this widening. Ment et al. [10] proposed that subarachnoid widening in the infant is a non-specific response and is probably more common than thought. Perhaps the term "external hydrocephalus" should therefore not be applied to children who show no evidence of significant ventricular dilation or signs of raised intracranial pressure.

In a recent review of hydrocephalus, Mori [12] suggested that external hydrocephalus should be excluded from the classification in view of the confusion and con-

troversy associated with its definition and clinical implications.

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Pre- and neonatal hydrocephalus in the Middle East: experience in Qatar

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Abstract. In a retrospective study, all cases of hydrocephalus diagnosed antenatally or within the first 10 days of life during the period 1986–1989 were reviewed. Thirty-four cases were diagnosed antenatally and 31 after delivery. Among the last, 13 were hemorrhagic. In 17 cases a meningomyelocele was present. In 12 cases other malformations outside the nervous system were observed. This represents an incidence of 157/100000 live births for hydrocephalus and 41/100000 for meningomyelocele. All cases were compared against a control group that had normal antenatal ultrasound findings at the same time (35 cases), and against a second control group consisting of 53 women with five or more normal pregnancies at the time, and all normal babies. The differences are evaluated and their significance and implications for the future discussed.

Key words: Hydrocephalus – Antenatal – Postnatal – Incidence – Middle East

The incidence of a particular disease is seldom a worldwide uniform phenomenon. Different causes and methodologies are in some cases definitely, in others presumably related to the variations found. Population characteristics, environmental influences, socioeconomic conditions, and genetic background are among the well-known ones [3–5, 9, 14].

One consequence of this variability is that, in any specific study, figures from areas other than the one under investigation study are useful for comparison, better understanding, and possible explanations, but should never be used to replace the actual findings in the region under scrutiny. Furthermore, the actual knowledge of a particular incidence is of the utmost importance in health care planning.

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Qatar is a young state, with most of its tremendous development achieved in the last 20 years. It seemed to us, involved in the care of pediatric neurosurgical patients, that one important basic step should be to find out as precisely as possible the incidence and characteristics of hydrocephalus within the country, as this, together with trauma cases, comprises the majority of our pediatric case load. All relevant information relating to hydrocephalus, diagnosed antenatally or in the immediate postnatal period, from January 1, 1986, to December 31, 1989, forms the basis of this report.

Certain characteristics of the State of Qatar made this task possible as well as desirable. They are: small size (11437 km^2); a single medical system freely available to all the population; prenatal, natal, and postnatal care restricted to one fully equipped medical center, and a central statistics organization that provided information to double-check the figures we obtained from hospital records.

Material and methods

All the records of patients discharged from Hamad General Hospital with the diagnosis of hydrocephalus during the period January 1, 1986, to December 31, 1989, were reviewed. Only cases in which the original diagnosis was made either prenatally or in the neonatal period were considered. This information was checked and complemented when necessary with a review of the Diagnostic Ultrasound Section records and those of the Neonatology Unit registry (Intensive Care and Intermediate Care), where all these newborn babies are admitted after delivery. The neonatal period, for the purposes of this study, was considered as the 10 days following delivery.

Hydrocephalus was diagnosed by a combination of ultrasonography (US), computerized tomography (CT), and clinical findings, including surgical confirmation. For inclusion in this study, confirmation by two of these methods had to be present. Hydrocephalus was considered to be present when the LVW/HW, BPD, HC and cortical thickness were beyond established normal values for age [10]. In all cases simple visualization of the ventricular system was enough, rendering all measurements complementary rather than diagnostic.

All cases were included, regardless of symmetry and number of ventricles enlarged. No case was seen with unilateral ventricular enlargement. Associated malformations were registered. They were stated as verified after delivery.

Repeated antenatal ultrasonograms were performed if the initial findings were borderline or moderately abnormal. Postnatal ultrasonograms were available for all cases.

Up to June, 1990, antenatal US was performed mostly, but not exclusively, in high-risk pregnancies or by reason of obstetrical considerations at the time of examination. Since that date, all pregnant women being followed at the obstetrics clinic are routinely evaluated by US at 18 weeks' pregnancy. This still represents a special group, as women with significant past medical or obstetric history tend to seek obstetric advice earlier and regularly during their pregnancies. Nevertheless, about 80% of pregnancies are regularly followed.

All CT scans were postnatal and confirmed the US diagnosis. The additional value of CT was mainly to evaluate, if possible, the type of hydrocephalus, the anatomy, and changes in the parenchyma.

Clinical criteria included a head circumference at least 2 standard deviations above the normal values for age (Growth Charts, National Center for Health Statistics), suture spread, or rapid head growth with increase or development of suture spread. All cases surviving delivery showed clear evidence of progressive hydrocephalus. Cases of stable ventricular dilatation diagnosed in the antenatal period and confirmed stable after birth, without clinical manifestations or associated anomalies, were excluded from the present series.

A control group was formed out of all consecutive cases that had a normal antenatal ultrasonogram performed during the same period of time. A second control group, called "normal-normal," was formed from women who delivered a normal baby within the same period of time and had five or more pregnancies (including the one resulting in the present delivery) with normal babies delivered. No women were included in more than one group.

For statistical calculations, the χ^2 test with the Yates correction was used.

General statistical information regarding the State of Qatar was obtained from the Vital Statistics Annual Report, Ministry of Public Health, Preventive Health Department.

Results

A total of 65 hydrocephalics were collected, with 34 cases diagnosed antenatally (AN), and 31 after delivery (PN). Out of this last group 13 cases were of hemorrhagic hydrocephalus (HH). Mean gestational age at the time of diagnosis in the AN group was 29.2 (14–36) weeks.

Meningomyelocele was present in 17 cases, almost equally distributed between the AN and PN groups. Other malformations related to the nervous system were present in 4 cases of the AN group; they were 2 cases of agenesis of the corpus callosum and 2 of holoprosencephaly. Malformations other than in the nervous system were present in 8 and 4 cases respectively.

Only 2 cases of isolated meningomyelocele were observed. The control group included 35 cases. The normal-normal group included 53 cases (Tables 1, 2).

The only statistically significant differences were the blood group distribution, with HH cases having a high incidence of B group ($P<0.05$), and a low incidence of O group ($P<0.02$), and the much lower incidence of abnormal past history in the normal-normal group compared with that of any other group, including the control ($P<0.01$). Hydramnios was observed only in the AN group.

Statistical comparison within the data in Table 2 showed several significant differences:

1. The incidence of spontaneous normal deliveries was higher in the control group than in the AN and PN groups ($P<0.02$ and 0.05).

2. The incidence of breech deliveries was higher ($P<0.001$) in the HH than in any other group.

3. Prematurity was more frequent in the HH group ($P<0.001$).

Table 1. Maternal data. AN, Hydrocephalus diagnoses antenatally; PN, hydrocephalus diagnoses postnatally; HH, hemorrhagic hydrocephalus

	AN ($n=34$)	PN ($n=18$)	HH ($n=13$)	Control ($n=35$)	Normal-normal ($n=53$)
Nationality					
Qatari	15	7	5	17	26
Pakistani	4	4	2	5	12
Egyptian	1	1	3	2	2
Yemeni	5	0	0	1	2
Other	0	6	3	10	11
Age (years, mean and range)	28.5 (19–41)	27 (20–35)	28 (20–38)	27 (20–38)	30 (23–40)
Pregnancy number (mean and range)	5.5 (1–13)	4.9 (1–9)	3.1 (1–9)	4.4 (1–13)	7.5 (5–11)
Abnormal past history	16	4	5	13	7
Blood group					
A	10	4	2	7	14
B	6	4	6	7	13
AB	2	2	2	2	5
O	15	7	1	19	19
Unknown	1	1	2	0	2
Hydramnios	21	–	–	0	0

Table 2. Case data

	AN ($n=34$)	PN ($n=18$)	HH ($n=13$)	Control
Term	14	11	4	35
Delivery				
Spontaneous normal	10	5	5	21
Spontaneous abnormal	0	0	0	0
Induced normal	10	4	0	7
Induced abnormal	2	0	0	2
Cesarean section	7	7	2	2
Breech	2	1	5	0
Abortion	3	0	0	0
Puncture	9	0	0	0
Sex				
Male	12	10	5	14
Female	18	7	8	21
Undetermined	4	1	0	0
Apgar score (mean and range)				
1 min	5.1 (0–9)	4.8 (1–10)	5 (0–8)	8.1 (1–9)
5 min	6.7 (0–10)	7.3 (1–10)	7.6 (0–10)	9.4 (4–10)
Weight (g) (mean and range)	2412 (1150–6600)	2484 (660–4660)	1119 (780–1520)	3136 (1450–4380)
Head circumference at birth				
90th percentile	9	9	0	2
75th percentile	3	1	2	6
50th percentile	2	0	5	8
< 50th percentile	0	4	3	12
Mean ± SD (cm) (range)	35.0 ± 5 (25–47)	38.4 ± 8 (28–56)	28.1 ± 3 (23.5–35)	34.3 ± 3 (31–38)
Unknown	20[a]	4	3	7
Meningomyelocele	8	9		
Other CNS malformation	4	0		
Other malformation	8	4		
Mortality				
Dead	11	10	4	0
Stillborn	4	0	0	0
Aborted	3	0	0	0

[a] Includes fetuses stillborn, aborted and dead shortly after delivery

Table 3. Mortality-related conditions in the AN group

	n	Dead
Puncture	9	6 (3 stillborn)
Other abnormalities	8	7
Meningomyelocele	8	3
Other CNS abnormalities	4	1

Table 4. Yearly distribution. ( ), with meningomyelocele

Year	AN	PN	HH
1986	5 (2)	5 (2)	2
1987	7 (1)	5 (4)	4
1988	13 (3)	5 (2)	3
1989	9 (2)	3 (1)	4

Table 5. Live births in the State of Qatar

Year	Births
1986	9 942
1987	9 919
1988	10 675 (107 home deliveries)
1989	10 659 (72 home deliveries)

4. Head circumference 75th and 90th percentile were more frequently seen in AN and PN groups ($P<0.01$) than in the rest.

5. Apgar scores and weight tended to be higher in the control group.

6. Head circumference was restricted to narrower limits within the normal range in the control group.

Fifty percent of all deaths in the AN-PN group occurred within the first 24 h after delivery, while 100% of the deaths in the HH group occurred 1 month or more after delivery. Out of those who died, two patients in the AN-PN group were treated and three in the HH group. No statistical differences in mortality were found in relation to nationality, maternal age, type of delivery, number of pregnancies, birth weight, presence of meningomyelocele, degree of hydrocephalus, or past history. On the other hand, mortality was associated with punctures and the presence of other abnormalities (Table 3).

The N-N group was not included in Table 2 because significative differences were already established by our selection criteria, as all deliveries as well as the babies had to be normal. One important point in this group was the fact than after the pregnancies and deliveries on which inclusion in the study were based, 13 new normal pregnancies and deliveries were registered, in one case 2 subsequent pregnancies with similar result. Only 2 abortions (within the first 8 weeks) were recorded within the period of observation. There were no significant differences when months or seasons were compared (Table 4).

Forty percent of all live births in the State of Qatar (Table 5) are Qatari. One hundred fifteen fetal deaths and spontaneous abortions have been registered for the year 1988, 3 cases of anencephaly and 2 of encephalocele among them. In 26 cases the cause was unknown. No hydrocephalus or meningomyelocele were reported. Qatari cases again constituted 40% (Tables 6, 7). No significant differences in regard to abnormal past history were found even when age, nationality, number of pregnancies, or abortion were considered (Table 8).

The TORCH test was performed in 18 cases and results found to be abnormal in 5. Chromosomal studies were performed in 10 cases and abnormal results were given in 1.

Table 6. Incidence of hydrocephalus and meningomyeloceles

Hydrocephalus AN + PN	52 cases in 41 195 live births 126 cases in 100 000 live births
Hydrocephalus HH	13 cases in 41 195 live births 31.5 cases in 100 000 live births
Meningomyeloceles	17 cases in 41 195 live births 41.2 cases in 100 000 live births
Encephaloceles	8 cases in 41 195 live births 19 cases in 100 000 live births

Table 7. Comparative incidence of hydrocephalus and meningomyeloceles per 100 000 live births [4–14]

	Hydrocephalus	Meningomyelocele
India	300	500
UK	176	280
Uganda	150	0
Qatar	126	41
USA	96	71
Wales	63	–
Japan	32	26

Table 8. Comparison of abnormal past history

	AN + PN ($n = 52$)	Control ($n = 35$)
Previous abortion	13	15
Diabetes	8	8
Previous hydrocephalus	2	2
Hypertension	2	0
Infertility treatment	2	0
Previous abnormal baby	3	1
Syphilis	1	0
Condyloma latum	1	0
Hypothyroidism	1	0
Febrile episode	1	0
Toxoplasmosis	1	0
Asthma	1	1
Thalassemia	0	1
Previous stillborn	0	1
Diabetes + previous abortion	3	2
Diabetes + previous hydrocephalus	1	1

Discussion

Hydrocephalus is still a rather complex condition, reasonably easy to diagnose but quite difficult to explain, understand and treat. Even some basic aspects of the physiology of the cerebrospinal fluid, intracranial blood volume and circulation and intracranial pressure are still obscure. From the clinician's point of view things are even more complicated, as questions about etiology, evolution, prognosis, when, how and why to treat are still without definitive and satisfactory answers [4, 5, 9, 12, 13]. Our attempt was aimed at answering very basic and simple questions: How many? What characteristics? What can we learn about it? What can we do about it?

Studies in rather small communities have been recommended [3]. Our incidence figures are within the ranges of previous reports and closer to the higher values [4, 7, 14]. The importance of our figures resides in the fact that they combine the advantages of a hospital approach with a nationwide approach, as almost all deliveries and certainly all babies are cared for in a single medical facility. The importance of such a method has been discussed before [15].

In Qatar, the incidence of meningomyelocele is lower than the incidence of hydrocephalus. A similar tendency has been reported from the USA and Japan, although the difference in Qatar is more marked. There are two alternative explanations for this finding. One is the time limit for our inclusion of PN cases. Some children with meningomyelocele may develop overt hydrocephalus quite some time after birth and repair. However, only two cases of "isolated" meningomyelocele were seen during the same period; should they become hydrocephalic, their inclusion would not significantly modify the incidence. The other possibility is that the incidence of hydrocephalus not associated with meningomyeloceles is higher in our population. Actually, there is a striking difference if we compare our figure of 38% with previous reports of 16% [1, 3–13]. No such difference is found comparing the incidence of meningomyeloceles in the same series, but a large difference (30%–60%) is found again if other malformations are considered. The usual objection that antenatal groups tend to have false negatives does not explain the difference as it remains large whether we use only antenatal or antenatal plus postnatal figures. Finally, it is possible that hydrocephalus, anencephaly, and meningomyeloceles have a unique and independent relationship with etiological factors. This contention is supported by the reported independent variation of their incidences in relation to geographical areas, maternal age, and season [3]. Unfortunately, the number of our cases is not large enough to allow meaningful comparisons when the group is divided up according to other specific diagnostic criteria, besides the fact that some of these criteria are controversial and not easy to apply. Our mortality figures are similar to those of Hudgins et al. [8], but lower than the reported values of Cochrane et al. [2]. As expected, associated anomalies and punctures are highly related to mortality. We had a lower incidence of fetal deaths including still births. As most of the neonatal deaths occurred within the first 24 h, they may reflect not only the condition, but also the treatment policy.

No seasonal or monthly variation was found, nor any decrease in overall incidence of hydrocephalus, as reported in other areas [3]. However, in the year 1988, the incidence rose to 34%. This may well represent one of those episodic rises described as "epidemic" [6]. Longer observation periods will be required to verify this hypothesis. If the mothers are scrutinized, some interesting differences to previous reports were found [15]. No ethnic differences were apparent, although it must be recognized that it is hard to evaluate how similar or different a Qatari and a Pakistani are from each other, compared to a Puerto Rican and an American. It was also surprising to note the blood group difference in the HH cases, which cannot be explained by a different racial distribution.

It has also been suggested that a low socioeconomic level is associated with a higher incidence of hydrocephalus [15]. In our population, Qatari women represent the upper class, but the statistics relating to them are similar to those for the other nationalities. They simply reflect the population distribution of pregnant women. Our normal-normal group was collected in order to see whether there was any difference between women who consistently had normal pregnancies and delivered normal babies as compared even to the original control group. Five pregnancies was chosen as the lower limit, as this was the average number of pregnancies in the other groups. We considered that the control group reflected a limited set of environmental and temporary circumstances, while the normal-normal group represented a stable characteristic. The only significant difference was the low incidence of abnormal past history: in other words, the women in the latter group were healthier than the rest. Two interesting conclusions can be drawn from this finding. One is that perhaps these women represent a "genetically privileged" group. The other is that perhaps, in addition to the well-known causes of fetal malformations, any other important past medical event carries a potential risk if the required unfortunate circumstances are met. Quite probably this is the coincidence of any medical event in a genetically "unprivileged" mother. Geographical or environmental factors seem less important, as the differences between the AN, PN and control groups were not significant. The fact that 14 new normal pregnancies and newborns were seen within a 4-year period lends support to this hypothesis, because these mothers were exposed again to the environment without changing their pattern.

Regarding the babies, the findings are in accordance with previous publications and within expectations. The poor prognosis of the AN and PN groups as a whole also applies in the Middle East generally. Hemorrhagic hydrocephalus, constitute a separate group with head sizes, Apgar scores, birth weights, gestational age, and type of delivery showing differences, that, although statistically not significant within our values, point to a different tendency. Such a tendency could be the expression of a predominantly obstetric noxa, as suggested by the higher number of breech deliveries. Nevertheless, intrauterine hemorrhages have been recognized as an etiologic factor [11], posing the question whether all the above-mentioned characteristics are secondary to such an episode, and a cause of the obstetric difficulties, rather than their consequence.

Finally, we learnt from our results that the problem is of significant magnitude and seriousness, and warrants the formulation of norms for more aggressive prenatal monitoring in order to detect all pregnancies potentially at risk. The concept "high-risk pregnancy" must be enlarged to include almost any significant past medical event, as for the time being we have no way to identify in advance the hypothesized "genetically privileged" mothers. More detailed ultrasonographic diagnosis should be achieved to confirm the real incidence of isolated hydrocephalus. This more accurate diagnosis should lead to a rational and planned management policy, as suggested elsewhere [13]. Our normal-normal group should be subjected to an in-depth genetic evaluation as well as a careful search for other low-risk characteristics.

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Central nervous system and renal investigations in patients with Lowe syndrome

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Abstract. We describe three patients with Lowe (oculocerebrorenal) syndrome, emphasizing primarily the central nervous system and renal pathology. Using magnetic resonance imaging, we noted diffuse high T2 signals periventricularly, indicating significant white matter destruction, which may be responsible in part for the mental retardation, seizure disorder, hypotonia, and areflexia observed in the patients. In contrast to previously published reports, there was minimal renal tubular dysfunction; however, proteinuria was significantly increased in all patients. We believe that the observed proteinuria is primarily the result of glomerular pathology rather than renal tubular dysfunction and may represent a net loss of negative charges within the glomerular filter. This loss of charge may be linked to the increased excretion of glycosaminoglycans in the urine.

Key words: Lowe syndrome – Central nervous system – Mental retardation – Cataracts

Lowe (oculocerebrorenal) syndrome, first described in 1952 [15], is characterized by congenital cataracts, growth failure, hypotonia, mental retardation, and areflexia or hyporeflexia. Progressive renal tubular dysfunction, often resulting in acidosis, proteinuria, phosphaturia, aminoaciduria, and rickets, has been reported [13, 17]. In addition to increased renal amino acid loss, an intestinal amino acid transport defect and a derangement of ornithine metabolism have been described [3, 20]. Although the basic biochemical defect in Lowe syndrome is unknown, it has been suggested that a defect in connective tissue metabolism [10, 11] or a mitochondrial abnormality [7] may be involved in the pathogenesis of Lowe syndrome.

Lowe syndrome is inherited as a recessive X-linked disorder. The Lowe syndrome gene is linked to the Xq24-q26 region of the X chromosome [21, 22, 25]. It has been suggested that the DXS17, DCS11, DXS87, and DXS42 are located on the proximal side and DXS86 and DXS10 on the distal side of the Lowe syndrome locus [23].

This report describes the clinical variability of three patients with Lowe syndrome and highlights their central nervous system and renal manifestations.

Offprint requests to: S. M. Pueschel

Case reports

Patient 1

W.S. is a 19-year-old man with Lowe syndrome. He was born to a 28-year-old gravida III, para II, female. W.S.'s mother apparently was exposed to rubella during the 15th week of gestation, but she did not have any clinical symptoms compatible with rubella. Both acute and convalescent rubella titers were 1:40. At full term, W.S. was delivered vaginally in the vertex position. The Apgar score at 1 min was 9. W.S.'s birth weight was 3350 g. At the time of birth a calcaneal deformity of both feet, micrognathia, hypotonia, a generalized petechial rash, and bilateral cataracts were noted. During the subsequent days W.S. developed a harsh grade III/VI systolic murmur. The electrocardiogram, however, was normal and subsequent examinations did not mention cardiac symptoms or abnormal cardiac auscultatory findings. At the ages of 20 and 24 months, respectively, W.S. underwent aspiration of the cataracts. When he was 2.5 years old, W.S. developed herpetic keratoconjunctivities of the left eye, which resulted in a scar at the lower section of the cornea. At the present time W.S. is considered to be legally blind, yet he functions fairly independently in a familiar surrounding.

W.S.'s motor development was significantly retarded: he rolled over at 2 years, crawled at 6 years, stood at 9 years, and walked independently at 11 years of age. Similarly, his cognitive, language, and social developments were markedly delayed. W.S.'s seizure disorder started at the age of 15 years. Initially, he was treated with phenobarbital and later with diphenylhydantoin. Approximately 2 years ago the latter medication was discontinued and carbamazepine was administered instead with good seizure control. In addition, W.S. has arthritis of his left knee and is being treated with salicylates. Academically, W.S. is functioning at 2–3 grade level. His cognitive abilities are in the moderately mentally retarded range. W.S. often exhibits autistic-like behavior, atypical hand movements, inappropriate vocal habits, and oppositional behavior. His communication skills are limited and perseverations and echolalia are noted.

Concerning the family history, W.S. is the youngest of three children in this family. His two older sisters enjoy good health. One

sister has been identified to have lenticular opacities and may be a carrier of Lowe syndrome. There are no members in this family who are known to have Lowe syndrome.

On physical examination W.S. is below the third percentile in weight, height, and head circumference. He wears heavy glasses and has an inferior stromal scar at the left cornea. There are bilateral sector iridectomies superiorly and bilateral aphakia. Apparently he does not have any vision in the right eye and he has significant visual impairment in the left. The intraoral structures reveal a narrow high-arched palate with a significant overbite. Respiratory, cardiovascular, and gastrointestinal systems are all intact. His genitalia are that of a normal postpubertal male (Tanner stage IV) with only one testicle descended. There is a left lumbar prominence, indicating mild scoliosis. His muscle tone and muscle strength are reduced. Deep tendon reflexes could not be elicited. W.S. walks with a broad-based gait. Genu recurvatum and calcaneovalgus position of his feet are observed. Radiographs of the tibias show a disturbance affecting the diametaphyseal regions of the tibias compatible with osteomalacia, but signs of overt rickets and the Looser zone are absent.

An electroencephalogram indicated a spike and wave focus over the mid- to anterior temporal regions with a poorly organized background. A magnetic resonance imaging study revealed diffuse white matter destruction in the periventricular area. Most laboratory studies were within normal limits, including complete blood count, serum glutamic oxaloacetic transaminase (SGOT), blood urea nitrogen (BUN), Na, K, Cl, CO_2, Ca, P, Mg, creatinine, uric acid, thyroxine, thyroid-stimulating hormone, and albumin. His serum carnitine levels were normal, the total carnitine concentration was 45 nM/ml and the free carnitine was 34 nM/ml. His serum sialic acid concentration was low, the total sialic acid level was 247 nM/mg creatinine and the free sialic acid level was 52 nM/mg creatinine. His serum cholesterol was elevated at 253 mg/dl. A 24-h urine collection contained 4.6 g protein, 85 mg calcium, 472 mg phosphorus, and 0.5 g creatinine. The renal function studies are summarized in Table 1. W.S. has significant aminoaciduria with increased excretion of lysine, histidine, hydroxyproline, threonine, serine, proline, glycine, alanine, valine, cystine, tyrosine, phenylalanine, and homocystine. His nonsulfated disaccharides are 47.5% (normal mean is 13.5%), 6-sulfated disaccharides 0.6% (normal mean is 45.0%), and 4-sulfated disaccharides 51.8% (normal mean is 39.7 %).

Patient 2

D.C. is a 7-year-old boy who was born to a then 23-year-old gravida I, para 0, female. His mother is a known carrier of Lowe syndrome since she has two uncles and two brothers with this disorder and she has been known to have bilateral cataracts since the age of 15 years (see Fig. 1). D.C.'s mother had intermittent vaginal bleeding during the first 4 months of gestation. At the 16th week amniocentesis was attempted but was unsuccessful and the mother refused to have a second amniocentesis performed. At 33 weeks of pregnancy she went into active labor. Double-footling breech was diagnosed and a cesarean section was performed. Apgar scores were 6 and 8 at 1 and 5 min, respectively. The infant appeared to be hypotonic. Bilateral cataracts were identified. The neonatal period was complicated by necrotizing enterocolitis, hyperbilirubinemia, and feeding difficulties. At 4 weeks of age cataract extraction was performed on the left eye and at 6 weeks of age the cataract was removed from the right eye. D.C.'s motor milestones were delayed, he started to walk when he was 2.5 years of age. He had been enrolled in an early intervention program from birth to 3 years of age, subsequently attended a preschool special education program, and is now partially mainstreamed in public school. D.C.'s intellectual functioning is in the mildly mentally retarded range. D.C. does not have a seizure disorder.

On physical examination, D.C.'s height and weight are below the third percentile. Although previous head circumference measurements were below the third percentile, during the past 3 years his head circumference has gradually increased and at the present time it is at the 25th percentile. His head appears relatively large with frontal bossing. D.C. wears heavy glasses and has congenital nystagmus a high arched palate, and hypoactive deep tendon reflexes. The remainder of the physical examination is normal.

Laboratory studies revealed normal cholesterol, BUN, creatinine, serum protein, SGOT, Na, K, Cl, Mg, Ca, and P. He has proteinuria of 1.2 g/24 h, and generalized aminoaciduria. Other renal function studies are presented in Table 1. An MRI showed a large subarachnoid cyst measuring 2.5 × 3.0 cm and bilateral severe periventricular leukomalacia. A radiograph of the hand revealed a delayed bone age (3.5 years) and there was no evidence of a demineralizing process.

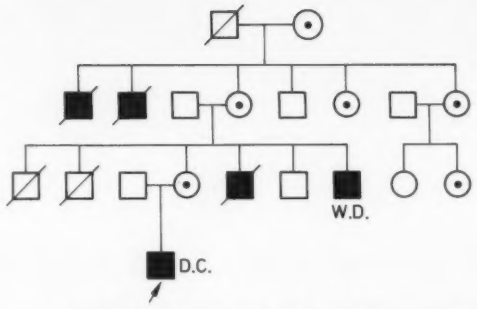

Fig. 1. Pedigree of family D, including index patient D.C. and his uncle W. D. ■ Affected person, ⊘ deceased, ⊙ carrier

Table 1. Renal function studies

Function	Patients			Normal values
	W.S.	D.C.	W.D.	
Creatinine clearance (ml/min/1.73 m^2)	57.5[a]	83.0[a]	94.8	>90
Urine protein/creatinine ratio	5.3[a]	4.6[a]	3.6[a]	0.15
Fractional sodium excretion	<1%	1.6%	<1%	<2%
Urine calcium/creatinine ratio	0.15	0.48[a]	0.12	<0.2
Tubular reabsorption of phosphate	61%	81%	78%[a]	>80%

[a] Abnormal value

Patient 3

W.D. is 18 years of age; he is D.C.'s uncle (see Fig. 1). W.D. was born to a gravida VII, para V, 32-year-old female. The pregnancy was uncomplicated and the delivery took place at full term. He was noted to have bilateral cataracts shortly after birth. W.D. was institutionalized during his first few years of life. He was adopted at the age of 7 years. His early development was significantly delayed. W.D. is profoundly mentally retarded, nonverbal, and nonambulatory. He had cataract extractions during the first year of life. His vision is significantly impaired and he is legally blind. At the age of 10 years W.D. had his first seizure. Initially, he was administered phenobarbital and later diphenylhydantoin was added to the therapeutic regimen. During the past few years he has been treated with valproic acid and carbamazepine. In spite of adequate therapeutic blood levels of the seizure medications, W.D. continues to have intermittent, generalized tonic-clonic seizures. He also has brief episodes of staring into space with head and arm drops. When W.D. was 9 years of age, he underwent heel cord lengthening of the left

leg. At the age of 13 years a femoral rotational osteotomy was performed because of a dislocated left hip.

On physical examination W.D. appears small with height, weight, and head circumference below the third percentile. W.D. has sunken eyes, oscillating eye movements, and asymmetric facies. His respiratory, cardiovascular, and gastrointestinal systems are normal. The right testicle is palpable in the scrotum and the left testicle is undescended. W.D. is hypotonic. He is unable to walk without assistance. The deep tendon reflexes are difficult to elicit in both upper and lower extremities. His plantar responses are flexor. A mild scoliosis is present.

W.D.'s MRI showed moderate dilation of the supratentorial ventricular system, most pronounced in the occipital horn of the left lateral ventricle. There was a diffuse high T2 signal of the periventricular white matter, yet the white matter of the cerebellum and brain stem were normal. W.D.'s electroencephalograms have always been grossly abnormal with prominent slowing of the background rhythmic pattern, excess of spikes and slow waves, and at times spike wave groups appearing anteriorly. Laboratory studies including BUN, creatinine, uric acid, cholesterol, alkaline phosphatase, albumin, total protein, SGOT, Na, K, Cl, CO_2, Ca, and P were all normal. There was generalized aminoaciduria and 2.3 g of protein in a 24-h urine collection was noted. Other renal function studies are shown in Table 1. A roentgenogram of the right knee revealed diffuse osteoporosis.

Discussion

Over the past four decades, since Lowe and coinvestigators' first description of the syndrome which bears his name, more than 150 case reports of Lowe syndrome had been published in the medical literature. Although the main characteristics including congenital cataracts, mental retardation, growth retardation, and renal tubular dysfunction have been studied in the past, there is marked heterogeneity and this report points out some of the clinical diversity observed in Lowe syndrome.

As usually noted in Lowe syndrome, our patients were also born with congenital cataracts. W.S. was first thought to have congenital rubella since his mother was apparently exposed to German measles during the 15th week of gestation and the infant was born with a hemorrhagic skin rash. However, W.S.'s mother did not have any symptoms compatible with rubella and the convalescent rubella titer did not show an increase over the acute titer. In addition, the patient's subsequent renal dysfunction characterized by aminoaciduria, proteinuria, and mild phosphate wasting, the presence of normal hearing ability, the white matter involvement of the brain, and one of W.S.'s sisters having lenticular opacities, suggesting carrier status of Lowe syndrome, all make the diagnosis of congenital rubella very unlikely.

Musculoskeletal abnormalities

Several reports in the literature focus on musculoskeletal abnormalities in Lowe syndrome [1, 6, 12, 19]. All our patients had significant delays in their gross motor development. W.D. is essentially nonambulatory. He has had tight heel cords, needed heel cord lengthening, and also required femoral rotational osteotomy. D.C. had moderate motor developmental delay and walked independently at 2.5 years of life. W.S. had a severely delayed development and only started to walk at 11 years of age. Although W.S. was born with a calcaneal deformity of both feet requiring serial casting, it is unlikely that this could account for the observed significant motor developmental retardation. At the present time he has a mild lumbar scoliosis, genu recurvatum, and his feet are in a calcaneovalgus position. In addition, he has been diagnosed as having monoarticular arthritis.

Frank rachitic changes have not been observed in our patients, although some abnormal roentgenographic findings have been noted. W.D. and W.S. have radiological evidence of osteoporosis. Both of these patients have been maintained on anticonvulsants, which may have altered their vitamin D metabolism. In addition, these two patients exhibit mild renal tubular phosphate wasting. D.C. has had long-standing mild metabolic acidosis and hypercalcuria, which could account for some of the bone changes.

Neurological abnormalities

Mental retardation, hypotonia, and areflexia or hyporeflexia that are invariably observed in individuals with Lowe syndrome were also noted in our patients. All our patients are significantly cognitively limited, yet they differ in the degree of intellectual functioning: W.D. is profoundly, W.S. is moderately, and D.C. is mildly mentally retarded. All three patients had various degrees of hypotonia in infancy which became less pronounced as they advanced in age. The deep tendon reflexes are not elicitable in two patients (W.S. and W.D.) and they were hypoactive in D.C.

Seizures are noted in two of our three patients (W.S. and W.D.). W.S.'s seizures began when he was 15 years of age and are clonic-tonic in nature. W.D. had his first seizure when he was 10 years old. He has a mixed type of seizure disorder, including generalized tonic-clonic convulsions and in addition absences and minor motor seizures. W.D.'s convulsions have been difficult to treat effectively. The electroencephalograms of the two patients with seizures revealed spike and wave discharges with poorly organized background. D.C. is only 7 years of age, and there is the possibility that he still may develop seizures in the future.

Of significance are the results of the brain MRI investigations. All three patients showed white matter lesions in the form of diffuse high T2 signals periventricularly. The white matter of the cerebellum and brain stem, however, was normal. In addition, D.C. had a large subarachnoid cyst and W.D.'s supratentorial ventricular system was moderately enlarged. Charnas and coworkers have also observed diffuse and irregular foci of increased T2 weighted signal intensity [5]. Moreover, these investigators reported results of a nerve biopsy of a patient with Lowe syndrome displaying decreased numbers of myelinated fibers, normal myelination of remaining axons without redundant basal lamina, and no evidence of degeneration or regneration of neural tissue [5]. Patchy demyelinating processes of both cerebral and cerebellar white matter have been reported by other investigators [8, 16, 18]. In contrast, Banerjee and coinvestigators did not find specific neuropathological abnormalities in patients with Lowe syndrome [2].

Renal manifestations

The renal effects of Lowe syndrome can vary considerably from patient to patient. Renal tubulointerstitial disease characterized by tubular atrophy, fibrosis, and dilation of the residual tubules is often observed. This is associated with variable amounts of tubular dysfunction, including proximal renal tubular acidosis and generalized aminoaciduria [4, 9]. What is less well appreciated and explained is the significant proteinuria observed in many of these patients. Although the proteinuria is nonorthostatic and may be heavy, these patients have not been nephrotic. Proteinuria can be observed when the glomerular filtration rate (creatinine clearance) is either normal or only mildly depressed. Van Acker and associates were among the first to describe subtle ultrastructural changes in glomeruli from patients with Lowe syndrome [24]. In their report, one patient had normal glomeruli under light microscopy, but using electron microscopy several significant abnormalities were observed. Glomerular endothelial cells were swollen, the number of endothelial slit pores was reduced, there was fusion of epithelial foot processes, and the glomerular basement membrane was thickened in some areas with scattered splitting of the lamina densa. Changes in the tubular structures were less noteworthy [24]. These ultrastructural glomerular findings together with increased proteinuria are consistent with a pathological process in which there is a net loss of negative charges within the glomerular filter. This loss of charge may be linked to losses of glycosaminoglycans observed in patients with Lowe syndrome [10, 11, 14, 26]. The proteinuria seen in our patients was associated with a mild-to-moderate fall in glomerular filtration rate in two of the three patients (W.S. and D.C.).

The patients presented in this report had normal serum concentrations of sodium, potassium, chloride, calcium, phosphate, magnesium, and total proteins. Apart from the generalized non-sulfated aminoaciduria, our patients demonstrated minimal signs of renal tubular dysfunction. Sodium handling appeared grossly appropriate as assessed by the fractional sodium excretion. Acid-base status was maintained in two of the three patients, but one patient (D.C.) exhibited a mild metabolic acidosis associated with hypercalciuria. Renal tubular reabsorption of phosphate was mildly decreased in two of the patients (W.S. and W.D.) and low-to-normal in one (D.C.).

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Intracranial cavernous angioma in the 1st year of life and a review of the literature

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Abstract. Three cases of symptomatic cavernous angioma occurring in the 1st year of life are presented. All three patients were treated with radical extirpation. Postoperatively, two of them improved, but the third died due to cerebral herniation secondary to recurrence of bleeding of the lesion. The clinical characteristics of cavernous angioma in the 1st year of life are briefly discussed and a review of the literature presented, including 16 previous cases operated on directly.

Key words: Cavernous angioma – Surgery – Literature review

In the present study, we report our experience with three cases of intracranial cavernous angioma in the 1st year of life. The clinical aspects of the lesion are discussed and a review of the literature is presented.

Case reports

Case 1

A 6-month-old boy was admitted on 2 August 1990 because of abrupt convulsive attacks. On admission, there were no abnormal findings on neurological examination except for motor weakness of the extremities on the right side. Computed tomography (CT) scan showed, in the left parietal lobe adjacent to the lateral ventricle, a well-defined, inhomogeneous hyperdense mass, 1.5 cm in diameter, partly with calcifications (Fig. 1, top left); the effect of contrast enhancement on the lesion was scant (Fig. 1, top right). Magnetic resonance imaging (MRI) revealed a homogenous, hyperintense mass, 1.5 cm in diameter, on T_1- and T_2-weighted images (Fig. 1, center left and center). In addition, proton imaging of the lesion clearly showed an inhomogeneous hyperintensity and an obvious hemosiderin rim (Fig. 1, center right).

A transcortical approach with parietal craniotomy was chosen, and microscopically a dark-red lesion, partially composed of hematoma, was totally removed. Histological examination of the specimen verified a hemorrhagic cavernous angioma. The patient's postoperative course was uneventful. After a follow-up period of 4 months, the patient is symptom-free, with no residual lesion except for a very small high-density spot on CT (Fig. 1, bottom).

Offprint requests to: N. Sakai

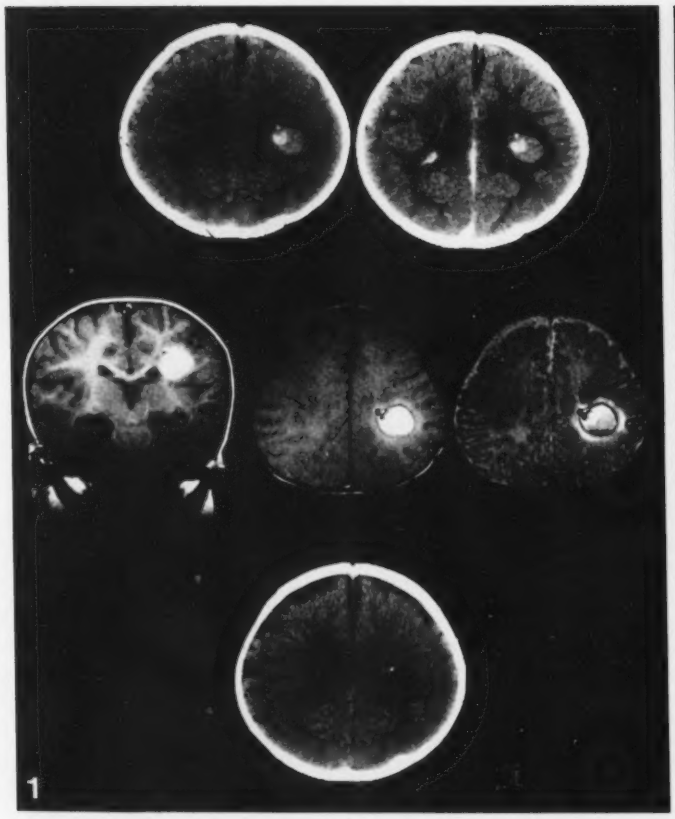
Case 2

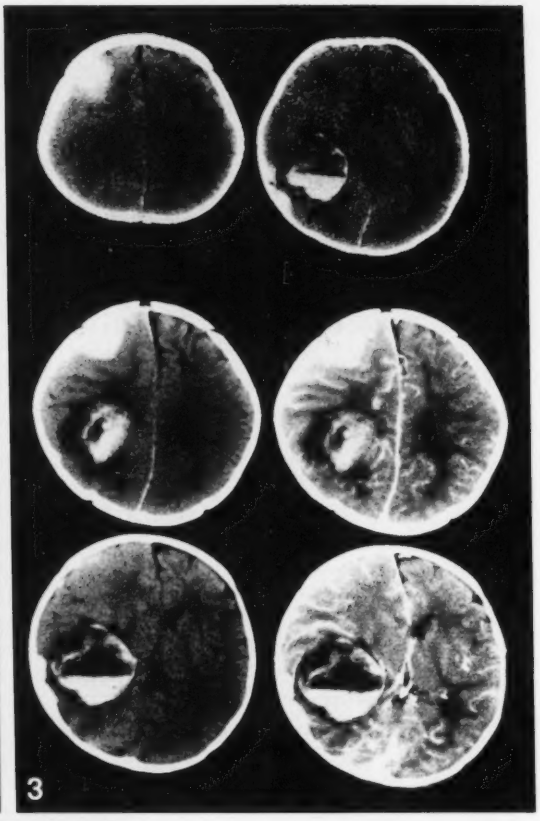
A 1-month-old boy was admitted on 14 July 1990 because of sudden inactivity and an increase of body temperature (39 °C). There were no abnormalities relating to his delivery. CT scan showed, in the right frontal lobe, a large inhomogeneous hyperdense mass, 6 cm in diameter (Fig. 2, left), with slight contrast enhancement, suggesting a cystic lesion with bleeding (Fig. 2, center). A frontal craniotomy was immediately carried out, and disclosed a large cortical mass with clearly defined limits; a large cyst containing brownish fluid was evacuated, and then the mass was completely removed with a small amount of bleeding. Histological diagnosis was a typical cavernous angioma. The postoperative course was uneventful. The patient is now symptom-free with no residual lesion on follow-up CT (Fig. 2, right).

Case 3

An 8-month-old boy was admitted on 26 May 1990 because of abrupt, repeated convulsive attacks originating in the upper extremity on the right side, and fever (38 °C). The patient was alert upon admission, although the anterior fontanel was tense.

CT scan showed two lesions: one was located in the right frontal region with a homogeneously high density, and was 2.5 cm in diameter (Fig. 3, top left); the other was located in the right parietal region with an inhomogeneously high density, and was 4 cm in diameter (Fig. 3, top right). CT was repeated 4 h after admission because the patient became drowsy and showed that both lesions had not noticeably changed in size, although the edematous changes around the lesion of the parietal lobe were increasing (Fig. 3, center). Furthermore, 2 h later, a fronto-parieto-temporal craniotomy had to be performed urgently due to the appearance of signs of uncal herniation on the right side. The preoperative CT scan demonstrated more clearly enhancement of the parietal lesion, 6 cm in diameter, and displacement of cerebral midline structure (Fig. 3, bottom). The two lesions were successfully extirpated in one stage. Histopathologically, cavernous angioma was verified in the two lesions. No improvement in the level of consciousness was seen postoperatively; the postoperative CT scan showed markedly edematous changes of the whole brain, following cerebral infarction in the territory of the right posterior cerebral artery. The patient died 1 month after the operation.





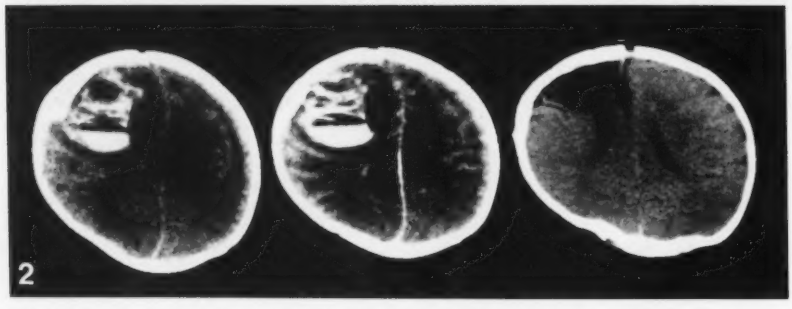


Fig. 1. Case 1. *Top*: Preoperative CT scans before (*left*) and after (*right*) contrast enhancement: in the parietal region, inhomogeneous hyperdense lesion 1.5 cm in diameter. *Center:* Preoperative MR images: homogeneous hyperintensity and hemosiderin rim. *Bottom:* Postoperative CT scan

Fig. 2. Case 2. Preoperative CT scan before (*left*) and after (*center*) contrast enhancement: in the frontal region, inhomogenous hyperdense mass with cystic component. *Right*: Postoperative CT scan

Fig. 3. Case 3. *Top:* CT scans before contrast enhancement at admission: in the frontal and parietal lobes, homogeneous and inhomogeneous hyperdense lesions respectively. *Center:* CT scans after contrast enhancement 4 h after admission: increase of the perilesional edema, although both lesion sizes were not changed. *Bottom:* Preoperative CT scans before (*left*) and after (*right*) contrast enhancement more than 2 h later: the size of the parietal lesion increased 1.5 times

Discussion

Recently, intracranial cavernous angioma has been reported frequently, its detection having been made easier by CT scan and MRI. It comprises 5–13% of CNS vascular anomalies [14]. Although this lesion has been found in all age groups [8, 16], it is exceedingly rare in the 1st year of life. In the literature available to us, we have been able to review only 16 cases that were histopathologically verified and directly operated on (Table 1). We have now added 3 of 26 cases from our own series. The age ranged widely from neonates to infants of 12 months, with a mean age of 5 months. There was no significant predilection as regards sex. Onset of symptoms consisted of convulsive attacks in 47.4% of the cases, an enlarged head in 31.6%, and various other symptoms. The lesion sites

Table 1. Literature cases histopathologically verified and directly operated cavernous angiomas

Author	Age	Sex	Onset symptoms	Location (size, cm)	Surgery	Outcome
McGuire et al. (1954) [9]	3 months	F	Head enlargement	Both lateral ventricles (1.8 × 0.8 × 0.5)	Partial removal	Improved
Sonntag et al. (1981) [17]	4 weeks	F	Head enlargement	Pineal region (1.5)	Total removal	Improved
Sugiyama et al. (1981) [18]	8 months	M	Generalized seizures	Left temporal (7 × 4 × 4)	Total removal	Cured
Iwasa et al. (1983) [5]	8 days	M	Head enlargement	Left lateral ventricle (3)	Total removal	Improved
Jooma et al. (1984) [6]	–[a]	M	Head enlargement	Cerebellar hemisphere	Total removal	Cured
Chadduck et al. (1985) [1]	4 months	F	Generalized seizures	Right lateral ventricle (4)	Total removal	Cured
Moritake et al. (1985) [11]	Neonate	F	Prenatal diagnosis	Right cerebellar tentorium (4 × 4.5 × 5)	Total removal	Cured
Yamasaki et al. (1986) [20]	2 months	F	Generalized seizures	Right frontal (3 × 3 × 3.5)	Total removal	Cured
Miyagi et al. (1987) [10]	2 months	M	Head enlargement	Right frontal (1.5 × 2 × 2)	Total removal	Good (hemiparesis)
Yasargil (1988) [21]	4 months	F	Swelling (left parietal)	Left parietal (6)	Total removal	Cured
Gangemi et al. (1989) [3]	9 months	F	Generalized seizures	Right frontal (large)	Total removal	Cured
	6 months	F	Head enlargement	Right frontal (large)	Total removal	Cured
Okada et al. (1989) [12]	4 months	F	Generalized seizures	Right frontal (6 × 4 × 2.5)	Total removal	Cured
Fortuna et al. (1989) [2]	12 months	M	Generalized seizures	Right ventricle (walnut size)	Total removal	Cured
Hubert et al. (1989) [4]	9 months	F	Hemorrhage	Left frontoparietal	Yes	–[a]
	10 months	M	Epilepsy	Right frontoparietal	Yes	–[a]

[a] Not described

were supratentorial in 85.7% and infratentorial in 14.3%. The most frequent sites in a total of 21 lesions, including 2 cases with multiple lesions (10.5%) were: frontal lobe (38.1%), lateral ventricle (28.6%), parietal lobe (14.3%), and cerebellum (10.5%). Of the 2 cases with multiple lesions, one was located in biventricular [9] and the other in frontal and parietal lobes of the right side (our present case 3). No significant laterality of the lesions was seen.

In general, if onset of symptoms and lesion sites of cavernous angioma in the 1st year of life are compared with those in other age groups [2, 8, 16], an enlarged head and lateral ventricle were most frequent, respectively. CT scans, performed in 14 cases with 15 lesions, showed a round hyperdensity mass with low contrast enhancement in the majority. Of all the lesions, 10 were homogeneous. Three of 5 lesions with inhomogeneous hyperdensity were accompanied by a large cyst [3, 12]. Such cyst formation seems to be characteristic of cavernous angioma in the 1st year of life. MRI was only performed in 2 cases. One is a case of Hubert et al. [4], in which the lesion showed an inhomogeneous high intensity, and the other is case 1 in our present series, in which the lesion demonstrated a homogeneous high intensity and a thin rim of hypointensity (hemosiderin rim). In general, the findings of CT and MRI of cavernous angiomas in the 1st year of life were similar to those in other age groups [7, 13, 19]. Surgical removal was total in the majority of cases, and yielded favorable results in all but 1 case, whereas a case of cavernous angioma with recurrence of bleeding has been reported, in which only the hematoma was removed [15]. However, our present case 3 had worsened within about 6 h after admission, and CT scans revealed an acute enlargement of the lesion, probably inducing cerebral infarction and edema. Such an abrupt hemorrhage of the lesion involving a cerebral vascular disorder should be noticed in the 1st year of life.

We can conclude that CT scan and/or MRI have made it easy to diagnose cavernous angioma easy, and radical extirpation of cavernous angiomas, even during the 1st year of life, is strongly recommended at an early stage especially in symptomatic cases, to avoid the risk of hemorrhage and of secondary enlargement or recurrence.

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Spontaneous spinal extradural hematoma in children

Report of three cases and a review of the literature

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Abstract. Three young children who presented with acute backache and rapidly progressive neurological deterioration were investigated and found to have spontaneous spinal extradural hematoma (SSEDH). They were operated on soon after the diagnosis had been confirmed. The present report highlights the fact that in children progressive weakness of nontraumatic origin should be investigated thoroughly and as early as possible. Patients with SSEDH should be operated on immediately, as this is a curable condition. The pertinent literature has been reviewed.

Key words: Spontaneous spinal extradural hematoma – Spinal hematoma – Quadriparesis – Paraparesis

Spontaneous spinal extradural hematoma (SSEDH) is a rare condition. Only 17 cases have been reported in children under 12 years. It is usually found in the cervicodorsal region in children [2, 14]. Back pain and progressive weakness of limbs with disturbance of bladder function is the common clinical picture [15].

Early diagnosis using imaging modalities and surgical intervention leads to a dramatic improvement in neurological functions in children. The management of three children with progressive weakness of nontraumatic origin is discussed in this report.

Case reports

Case 1

An 11-year-old girl was admitted with sudden pain in the nape of the neck radiating to the left shoulder and upper limb, and rapidly progressive weakness of both upper limbs followed by weakness of the trunk and both lower limbs. Two hours later, she developed retention of urine. Her neurological deficit progressed to a total loss of function below the C4 level over the next 16 h.

The baseline investigations, including a complete coagulogram, were normal. Plain X-ray films of the cervical spine did not reveal any abnormality. Iohexol myelography showed a partial extradural block from C5 to C7 posterolaterally on the left side. Cerebrospinal fluid (CSF) examination was within normal limits. Computed tomography (CT) scan showed a high attenuation lesion, most probably an epidural blood clot, in the same location (Fig. 1).

Exploration was performed 24 h after onset of the symptoms. An epidural hematoma was found after removal of C4–C7 laminae and a black jelly-like clot was removed. Histological examination revealed an organizing hematoma. No vascular malformation was seen. The patient showed very little improvement in the immediate postoperative period and only a slow recovery thereafter. Follow-up examination after 8 months revealed grade 4/5 power in both upper and lower limbs. Sensations and bladder function recovered to near normal.

Offprint requests to: V. K. Kak

Case 2

An 8-year-old boy had slipped in the bathroom about 1 month previously. Eighteen hours later, he started having low back pain and developed weakness of both lower limbs and urinary incontinence on the 3rd day.

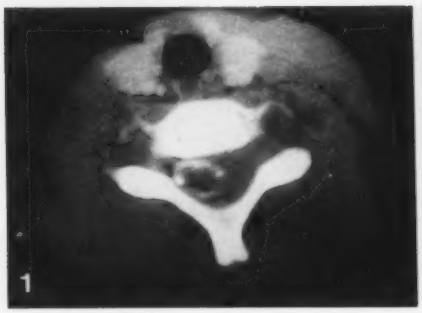
Examination revealed normal higher mental functions and cranial nerves. Power in the upper limbs was normal. He had grade 3/5 power in the right hip and knee, and grade 0/5 in the ankle and toes and the left lower limb. Joint position sense was impaired below the anterior superior iliac spine. Other sensations were normal. Deep tendon reflexes were absent in the lower limbs, as were plantar reflexes, which could not be elicited. Abdominal reflexes were present. Plain radiography of the dorsolumbar spine was normal. Iohexol myelography showed a partial extradural block at the L3–4 level. CT scan showed a hyperdense epidural mass causing an incomplete block at the D10 level (Fig. 2).

Exploration was performed 50 days after the onset of symptoms. At laminectomy from the D10 to L4 level, an epidural clot was found and evacuated. Histological examination revealed an organizing hematoma. No vascular malformation was seen. There was no significant return of function in the early postoperative period. Follow-up examination after 9 months revealed grade 4/5 power in the lower limbs with near normal bladder control.

Case 3

A 5-year-old boy, who had received a vaccination for diphtheria and tetanus 3 days before admission, presented with inability to bear weight on both lower limbs, retention of urine and progressive weakness of both the wrists and hands for 1 day prior to admission. He also had difficulty in breathing as well as pain in the upper back and neck.

Examination revealed normal higher mental functions and cranial nerves. The patient had grade 3/5 power in both upper limbs and 0/5 power in both lower limbs. He had intercostal muscle



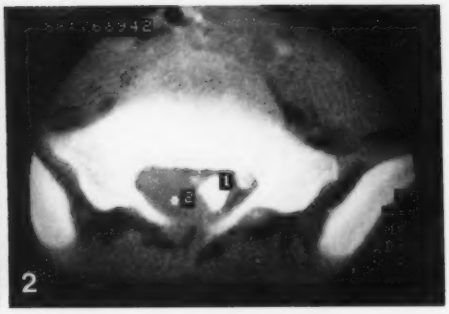


Fig. 1. Iohexol computed tomography (CT) of cervical region showing extradural block from C5 to C7

Fig. 2. Iohexol CT of lumbar region showing incomplete extradural block due to high attenuation lesion

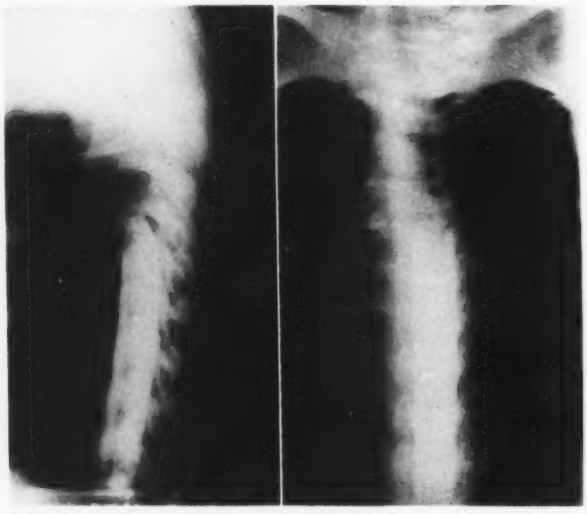


Fig. 3. Iohexol myelogram showing extradural block at D4

paralysis with bladder involvement. Sensations were lost below the D4 level. A diagnosis of acute Landry-Guillain-Barré syndrome was considered and the patient was put on ventilatory support for 5 days. Myelography performed at this time showed an extradural block at the D4 level from the posterior aspect (Fig. 3). As the patient had clinical involvement from C5 to D4 levels, a laminectomy from C5 to D4 was performed. An extradural hematoma, 1.5 cm thick, was seen extending from the C5 to D4 level and was evacuated. Histological examination revealed an organized hematoma. No vascular malformation was seen. The patient improved in the immediate postoperative period. Power in the upper limbs improved to grade 4/5 and in the lower limbs to 2/5. Sensations and bladder function returned to normal.

Discussion

SSEDH is a rare condition and only just over 100 cases have been reported to date [14]. It can occur at any age from 6 months to the 8th decade [2], but is most frequently seen in the middle aged or elderly [14]. The condition is uncommon in children and only 17 such cases have so far been reported in the literature [2]. It is commonly seen in the cervical and dorsal regions in childhood [14].

Though Jackson (1868) is credited as first reporting this entity, it was Blauby who first described this clinical condition in 1809 [9]. Johnston [2] was the first to report SSEDH in a child. SSEDH can be produced by: (1) rupture of valveless veins in the internal vertebral plexus with the slightest change of posture such as during sleep, turning movements, coughing, straining or due to Valsalva's maneuver [2]; (2) bleeding from abnormal vessels, e.g., angiomas [2, 4] or arteriovenous malformations (AVMs), whether cryptic or manifest [2, 11, 13]; (3) anticoagulant drugs, blood dyscrasias, e.g., hemophilia, leukemia, polycythemia vera, macroglobulinemia [2]; (4) metabolic changes during pregnancy [15]; (5) acute infections [2]; and (6) whooping cough [2].

Most authors consider that venous bleeding leads to the formation of SSEDH [14]. Pathological alterations of the vessel wall in vascular tumors and AVMs are known to lead to spontaneous and even multiple bleeding episodes and histological evidence of this bleeding can be seen in the vessel walls of AVM during microscopic examinations [13].

Cooper [3] and Schwartz et al. [12] concluded that "in the absence of gross trauma or bleeding diathesis, it is conceivable that this type of hematoma is related to an organised vascular abnormality or to transmission of increased intra-abdominal or intra-thoracic pressure to the epidural plexus initiating bleeding. However, it seems unlikely that this type of increased pressure would initiate hemorrhage in normal vessels." However, Foo and Rossier [6] found vascular malformations in 6 out of 158 and Müller et al. [11] in 4 of 5 cases of nontraumatic SSEDH.

Bleeding commonly occurs in the dorsal region and may spread up or down or even along the whole length of the spinal canal producing a rapid deterioration of neurological function. Spontaneous resolution of SSEDH, though extremely uncommon, does occur and results in clinical improvement [1, 5, 7]. There is an explanation for spontaneous recovery. Emery and Cochrane [5] have postulated that the oil-based contrast agent which they used acted by increasing the intrathecal volume dispersing the liquid component of hematoma, thereby relieving compression. Alternatively, they suggested that in cases where SSEDH had solid and liquid contents, removal of spinal fluid during myelography may promote dissipation of liquid hematoma into the epidural space.

About 35% of patients undergoing surgery for SSEDH recover their ability to walk [10]. The longer the delay in surgery, the worse are the results. The ultimate recovery depends on the duration, rapidity of cord compression and promptness of surgical decompression [10]. In contrast to the view of Karvounis et al. [8] that no recovery could be expected if decompression was per-

Table 1. Compilation of reports from the literature on patients less than 12 years of age [2]

Author	Age – sex	Site	Cause	Mode of onset	Deficit	Myelo/ CT	Oper- ation	Results
Johnston 1938	5 years-M	D8-12	Spontaneous (hemangioma)	1 year recurrent	Paraplegia	–	–	Autopsy
Shenkin et al. 1945	6 months-F	D7-10	Spontaneous	14 days	Paraplegia	D5-10	+	Cured
Carrea et al. II 1954	4 months-M	D9-L2	Birth injury	Intermittent	Paraplegia	L2	+	No improvement
Jones and Knighton 1956	12 years-M	C6-D2	Hemophilia	12 h	Paraplegia	–	+	No improvement (died after 6 months)
Maxwell and Puletti 1957	4 years-M	D2-4	Spontaneous	Acute	Paraplegia	–	+	Cured
Scott 1958	9 years-F	D1-4	Spontaneous	6 months	Paraplegia	–	+	Cured
Jackson 1963	1 year 3 months-F	D1-5	Spontaneous (scarlatina)	3 h	Paraplegia	–	+	Cured
Lepintre et al. I 1956	8 years-F	C7-D1	Spontaneous	12 h	Quadriplegia	–	+	Cured
Lepintre et al. II 1957	6 years-M	C7-D2	Fall (hemophilia)	2–4 h	Quadriplegia	–	+	No improvement
Lepintre et al. III 1969	1 year 6 months-F	C3-7	Spontaneous (minimal trauma)	7 days	Quadriplegia	–	+	Cured
Rubello and Dastur 1966	11 years-M	C3-7	Spontaneous	Acute	Quadriplegia	C3	+	Cured
Hehman and Norrell 1968	1 year 9 months-M	C3-D9	Spontaneous (minimal trauma)	5 days	Quadriplegia	–	+	Cured
Posnikoff 1968	2 years 6 months-F	C5-D5	Spontaneous	5 days	Quadriplegia	–	+	Cured
Amyot et al. 1969	1 year 4 months-F	C5-7	Fall	Weeks	L arm weakness partial block	–	+	Cured
Valladeres 1972	2 years 6 months-M	D3-5	Spontaneous	12 days	Paraplegia	D6	+	Cured
	2 years 9 months-F	C7-D3	Spontaneous (minimal trauma)	2 days	Quadriplegia	C7-D3	+	Improved
Present series	11 years-F	C4-7	Spontaneous	2 h	Quadriplegia	C5-C7	+	Improved
	8 years-M	D10-L4	Spontaneous (minimal trauma)	50 days	Paraplegia	D10-L4	+	Cured
	5 years-M	C5-D4	Spontaneous	3 days	Quadriplegia	C5-D4	+	Improved

formed 30 h after onset of symptoms, Müller et al. [11] felt that there was no relation between the degree of recovery and localization of the hematoma, patients' age or even the delay in surgery. One of their patients showed a good recovery following surgery 18 days after the onset of symptoms. We had similar experiences in cases 2 and 3 with good recovery following surgery after a delay of 50 days and 55 days, respectively.

Reviewing the available literature on cases of children under 12 years of age, we came to the conclusion that a good recovery occurs in children irrespective of age, duration of cord compression, rapidity of onset of symptoms or the force of compression (length and thickness of clot) (Table 1).

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Case report

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Intrinsic III ventricle craniopharyngioma

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Abstract. A case of intrinsic III ventricle craniopharyngioma in an 11-year-old girl is presented. Only five cases in children have previously been reported in detail. The intraventricular location of a craniopharyngioma originates from ectopic remnants and causes intracranial hypertension without hormonal or neurological disorders. The tumor was safely removed by the transcallosal approach, and we confirmed that the floor of the III ventricle was intact.

Key words: Pediatric craniopharyngioma – III ventricle – Transcallosal approach

Although the most common sites for craniopharyngioma are suprasellar areas, the tumor can also grow in many directions or in unusual sites, such as the nasopharynx [16, 19], cerebellopontine angle [1], posterior fossa and foramen magnum [21, 26], pineal gland [23], or within the chiasm [6]. The tumor frequently invaginates the floor of the III ventricle. Sweet [27] found that the neoplasm had invaded the ventricular cavity in 23 of the 40 patients operated on. Steno [25], analyzing 30 autopsies, observed 8 cases where the tumor had developed intraventricularly, and Konovalov et al. [13] operated on 85 children with tumors in extra- and intraventricular locations.

Conversely, purely intraventricular cases are rare. Mori et al. [18] found the tumor isolated in the III ventricle in 6 cases out of 155. Sweet [27] presented similar intraoperative evidence in 2 cases. Recently Yasargil et al. [28], reviewing 144 patients who had undergone microsurgical resection, mentioned 6 patients in whom the tumor was confined to the ventricle with few adhesions to the hypothalamus.

Thirty-three cases have been described in detail, including the first one presented as a probable case by Dobos [5] and the 5 most recent cases reported in the Japanese literature by Fukushima et al. [9]. Five of these cases were children: one 11-year-old male was operated on by occipital craniotomy after a ventriculoperitoneal shunt [18]. The second case was operated on at 10 years of age by ventriculocisternostomy and by frontal craniotomy 9 years later [11]. In these cases the tumor was subtotally removed. In the remaining 3 cases, 2 boys and 1 girl (aged 11–15 years), the tumor was removed using the lamina terminalis approach.

In the present case the tumor, which was totally confined to the ventricle, was successfully removed by means of the transcallosal approach.

Offprint requests to: A. Migliore

Case report

An 11-year-old girl had been suffering from headaches, nausea and vomiting for 1 month. On admission (24 June 1989) she was somnolent and confused. Neurological examination showed bilateral papilledema and marked bradycardia, but no other neurological changes. General physical examination was unremarkable. Skull radiography was normal with no evidence of calcifications or erosion of the sella turcica.

Computed tomography (CT) scan (Fig. 1) revealed a spherical hyperdense non-enhanced suprasellar mass. The tumor was occupying the III ventricle and the lateral ventricles appeared to be dilated secondary to obstruction of both foramina of Monro. A marked periventricular hypodensity was present.

Surgery was performed the next day. A right free bone flap centered on the coronal suture was removed, the frontal lobe was laterally retracted, and the corpus callosum was opened 2 cm in length, posterior to the genu. The foramen of Monro was found to be greatly dilated and the tumor appeared as a soft greyish-yellow, well-delimited mass, about 25 mm in diameter, occupying the III ventricle. The septum pellucidum was thickened and buckled upwards. After microsurgical dissection of the choroid plexus surrounding the posterior pole of the mass, the tumor, which was not adherent to the ventricular walls, was safely removed. The floor of the III ventricle was absolutely intact. The postoperative course was uneventful and no therapy with cortisone or thyroxine necessary.

The histological examination showed a typical craniopharyngioma (Fig. 2a, b). During long-term follow-up (28 months), no neurological, behavioral or endocrinological disorders were observed. Figures 3 and 4 demonstrate postoperative CT scan and magnetic resonance imaging (MRI).

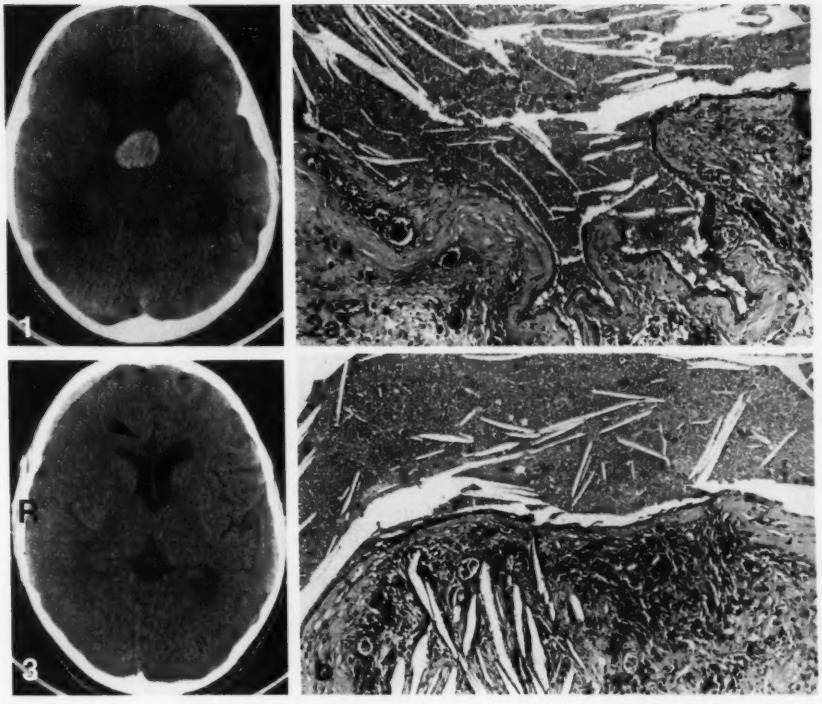

Fig. 1. Computed tomography (CT) scan shows a uniformly hyperdense non-enhancing mass occupying the III ventricle with resulting hydrocephalus from blockage of the foramina of Monro

Fig. 2a, b. Pathological findings showing the cystic feature of the tumor containing amorphous and necrotic debris areas with elongated cholesterine crystals (at the top of each figure part). The cyst is delimited by flattened pluristratified epithelium surrounded by chronic inflammatory tissue with giant cell reaction to cholesterol clefts

Fig. 3. Postoperative CT scan demonstrates the complete removal of the tumor and reduction of the hydrocephalus. The *arrow* indicates the transcallosal approach

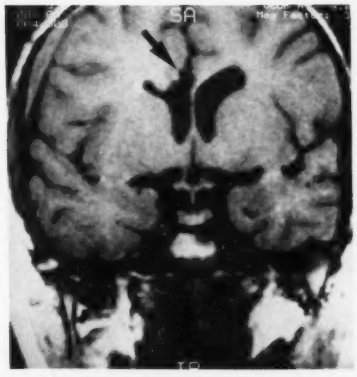

Fig. 4. Magnetic resonance imaging 8 months after the operation demonstrates, in addition to the surgical approach (*arrow*), the intact floor of the III ventricle, the patency of the suprasellar cistern and the normal appearance of the pituitary stalk

Discussion

Craniopharyngiomas intrinsic to the III ventricle are considered to be caused by ectopic remnants of Rathke's pouch [4, 10, 27]. Rush et al. [22] believe that these intraventricular tumors may result from upward growth of squamous cell nests from the floor of the III ventricle near to the tuber cinereum. Konovalov et al. [13] were able to demonstrate microscopic areas of the glial capsule of the tumor in the walls of the anterior part of the III ventricle; these areas represent a possible source of recurrences. Papo et al. [20] emphasized that the origin or craniopharyngioma from Rathke's pouch is still a controversial issue and that there is no clear-cut difference between neuroepithelial cysts with squamous epithelium attached to the floor of the III ventricle and Rathke's cleft cysts.

However, in all the cases described in detail, except in the two reported by Long and Chou [15], an intact hypothalamic floor has been observed. In our case, besides the absence of sellar abnormalities, surgical evidence and MRI clearly demonstrated that the floor of the III ventricle was intact, the suprasellar cisternae patent and the pituitary stalk normal.

An intraventricular tumor causes a syndrome of intracranial hypertension, as occurred in our case, generally without the hormonal and neurological disorders which are usual in suprasellar craniopharyngioma. Hemianopsia and diabetes insipidus were observed in the case reported by King [11] and bitemporal defects were present in the three cases observed by Klein and Rath [12]. King [11] emphasized that in tumors attached to the floor of the III ventricle the lamina terminalis may bulge and the chiasm may be forced downwards towards the tuberculum sellae.

CT does not provide a definite histological diagnosis, even if calcifications or cysts are present [8]. Usually the mass is contrast enhanced [9, 10, 14, 17], but in our case it was hyperdense and non-enhancing, as in the two cases described by Ferrara et al. [7]. Coronal CT and MRI are essential for establishing the intraventricular location of the tumor, and for providing information regarding the surgical approach.

We used the transcallosal approach, which provides easy access to the lateral ventricles and foramina of Monro with minimal retraction upon the brain and very

limited division of the corpus callosum. This procedure allowed us full control and permitted total removal of the tumor. The same approach was used by Long and Chou [15] in four cases, two of them previously operated on using the subfrontal approach, and by Japanease surgeons [9] in another two cases but with only partial removal of the tumor.

On the basis of their experience, many authors [2, 13, 24, 28] have stated that transcallosal and transcallosal interfornicial approaches provide more possibilities for evaluation and radical removal of tumors that impinge upon or enlarge the foramina of Monro, no matter what their nature, with minimal physiological consequences.

Other surgeons have used the subfrontal approach through the lamina terminalis [10–12], the transcortical route [3, 15, 17, 22] or both of these procedures [9]. The lamina terminalis approach offers easy access to the inferior part of the III ventricle and is preferable when the tumor is located in the lower portion of the ventricle and adherent to the floor. The suboccipital approach through the splenium of the corpus callosum has been used in one case [18] in which the tumor was located in the posterior half of the III ventricle, anterior to the pineal body.

Although intraventricular craniopharyngioma remains rare in children, more cases have been identified in the last decade, and our observation further emphasizes the need to consider this tumor in the differential diagnosis.

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XIX Annual Meeting of the International Society for Pediatric Neurosurgery

Seoul, Korea, 2–5 October 1991
(President: Fernando Rueda-Franco;
Chairman of the Meeting: Joon Ki Kang)

The 1991 annual scientific meeting of the ISPN was held in the convention hall of the Hotel Shilla in Seoul, Korea, on 2–5 October. The program, organized by Dr. Kiyoshi Sato, contained nine Scientific Sessions, five Symposia, two Special Lectures and a Breakfast Poster Session. Topics in the Symposia included moyamoya disease, skull base surgery, fetal anomalies and prenatal management, and low-grade astrocytoma.

A total of 173 participants (83 of them from Korea) were registered and provided plenty of discussion, especially on the subjects of management of fetal hydrocephalus, tethered cord syndrome, and skull base surgery in children. The President, Fernando Rueda-Franco, delivered the Presidential Address. The Meeting was extremely well organized and fruitful. After the scientific sessions every day typical Korean dinners were served.

The Business Meeting was held on the second day. New active members and one senior member were accepted.

Attendance at the 19th Annual Meeting of the ISPN

Country	Member	Non-member	Accompanying persons
Australia	2	1	
Austria	1		
Brazil	1		1
Canada	4		1
Chile	1		1
ČSFR	1		
France	3		1
Germany	2		1
India	4		
Italy	5		1
Japan	38		8
Korea	64	19	5
Mexico	1		
Rep. of China	1		1
Switzerland	1		
Turkey	1		
UK	4		1
USA	16	3	12
Subtotal	150	23	33
Total			206

Shizuo Oi (Kobe)

Fourth Postgraduate Course of the European Society for Paediatric Neurosurgery

Schloss Seggau/Graz, Austria, 8–11 October 1991
(Director: Dr. Rainer W. Oberbauer)

The purpose of this course was to support the development and recognition of pediatric neurosurgery in Europe. It was addressed to residents and young neurosurgeons interested in this subdiscipline of neurosurgery. The program, organized by Dr. R. Oberbauer, was arranged to provide open discusson with international experts and resulted in integration among participants.

A total of 41 lectures were given by 21 lecturers: 19 from Europe, 1 from the USA, and 1 from Japan. The scientific program consisted of 8 sessions covering hydrocephalus, epilepsy, spinal trauma, cerebrovascular diseases, spinal tumors, tumors of the lateral and III ventricles, intracranial cystic lesions, and surgery in the newborn. In each major session, case presentation and a round-table discussion were held.

A total of 93 participants were registered in this course, providing discussions in each session. The course was extremely well-organized and fruitful. After the lectures every day, typical Austrian dinners were served, over which all participants enjoyed exchanging views and extending friendships.

The ESPN will continue to hold annual courses in the future, always inviting leading lecturers in pediatric neurosurgery from around the world.

Shizuo Oi (Kobe)

Book reviews

Child's Nervous System CNS

Neuroendocrinological aspects of neurosurgery. Proceedings of the Third Advanced Seminar in Neurosurgical Research, Venice, April 30–May 1, 1987. Eds.: J. D. Pickard, F. Cohadon, J. Lobo Antunes. (Acta Neurochirurgica, Suppl. 47). Wien, New York: Springer 1990. 128 pp. with figures and tables. (ISBN 3-211-82160-0) DM 158.00.
This book, which is a bound supplement to *Acta Neurochirurgica*, reports the proceedings of the Third Advanced Seminar in Neurosurgical Research, held in Venice on April 30–May 1, 1987, and devoted to the "Neuroendocrinological Aspects of Neurosurgery."

The aim of the Conference was to bring together experienced basic scientists and neurosurgeons to provide a state-of-the-art assessment of the subject and to highlight an area of controversy such as that of neuroendocrinological/neurosurgical correlates. The first two chapters, which discuss the "neuroendocrine" anatomy of the hypothalamus and its physiology, respectively, provide the reader with an up-dated and infinite source of information on this rather mysterious region of the brain. The vascular supply to the pituitary-hypothalamic axis is then presented, followed by a clinical up-date on hypothalamic-pituitary control. These basic chapters, which justify "per se" interest in this book, are then followed by a series of short chapters that discuss in detail the problems correlated with fluid balance, which is under the control of the hypothalamus; for example, brain control of fluid balance and fluid balance disturbances in neurosurgery, with special reference to head trauma and subarachnoid hemorrhage. Moreover, an extensive chapter discusses in depth the non-surgical treatment of the pituitary-secreting adenomas responsive to medical treatment (such as prolactinomas or GH-secreting adenomas).

The overall quality of the book is high, although some chapters are imposing for their elevated value. Not only neurosurgeons will find interest in reading this volume, but also all of those (physicians, neurologists, endocrinologists, etc.) interested in the study of the hypothalamus-pituitary axis.

Massimo Caldarelli (Rome)

Rumack, C. M., Horgan, J. G., Hay, T. C., Kindsfater, D.: Pocket atlas of pediatric ultrasound. New York: Raven Press 1990. VI, 107 pp. with figures. (ISBN 0-88167-620-9) US $ 18.00.
Today the use of echoencephalography as a diagnostic, non-invasive tool is widely accepted. There are two main advantages in this technique: it is simple to perform and there is no X-ray. This latter characteristic makes the examination very acceptable for children, especially for evaluation of the brain. This pocket atlas shows the normal ultrasound anatomy of the brain, liver, adrenal gland, pelvis, testis, hip, kidney and spine in the child. Every scan is explained by a very interesting and accurate drawing of the plane of the section.

Special attention is given to ultrasound examinations of the brain, spine and hip, which are those mainly performed in children. Images were obtained by using both a 5.5 MHz sector transducer and, when possible, a 7.5 MHz transducer that gives a very clear description when a transfontanellar examination is performed. In this way an exact idea of the brain structures and the dimensions of the ventricular system can be obtained. This diagnostic tool is therefore most helpful in monitoring the development of hydrocephalus in the newborn, rather than performing a CT-scan which involves X-rays.

In conclusion, we would like to recommend this pocket atlas to medical students, residents, and all those who want to become acquainted with the diagnostic possibilities offered by this technique.

Enrico Marchese (Rome)

Announcements

Child's Nervous System CNS

The 25th Congress of the European Society for Paediatric Neurosurgery (ESPN) will be held in Berlin, 31 May–2 June, 1992. Topics: the pediatric spine – free topics. *3 June 1991 transfer to Prague.* **The XX Annual Meeting of the International Society for Pediatric Neurosurgery (ISPN)** will be held in Prague, 3–6 June 1992. Topic: unsolved problems of pediatric neurosurgery 1991/limits of pediatric neurosurgery. *For further information, please contact: ESPN* – Professor Mario Brock, Department of Neurosurgery, Free University of Berlin, Hindenburgdamm 30, W-1000 Berlin 45, FRG; *ISPN* – Professor Vladimir Beneš, Neurosurgical Department, Hospital of Pediatric Faculty, 15018 Praha Motol, Czechoslovakia.

The XXVII Meeting of the Canadian Congress of Neurological Sciences will be held at the Winnipeg Convention Centre, Winnipeg, Manitoba, 25–28 June 1992. *For further information, please contact:* Permanent Secretariat, Canadian Congress of Neurological Sciences, 810, 906 – 12 Avenue S.W., Calgary, Alberta T2R 1K7, Canada; tel.: (403) 229-9544; FAX: (403) 229-1661.

The 36th Annual Scientific Meeting of the Society for Research into Hydrocephalus and Spina Bifida will be held in Mainz, 15–18 July 1992. *For further information, please contact:* Dr. R. Bayston, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK; tel.: (0 71) 2 42 97 89; FAX: (0 71) 8 31 04 88.

The 6th Congress of the International Child Neurology Association (ICNA) and **the 1st Iberoamerican Congress of Pediatric Neurology** will be held in a joint meeting in Buenos Aires, Argentina, 8–13 November 1992. The official language will be English with simultaneous translation into Spanish. The program will follow the lines of previous ICNA meetings, including plenary lectures and symposia presented by leaders in the fields of pediatric neurology and the neurosciences. Free platform and poster presentations are encouraged. Satellite symposia and workshops are also being organized. *For further information, please contact:* Dr. Néstor Chamoles, General Secretary, Sarmiento 1562 4° "F", 1042 Buenos Aires, Argentina; FAX 5 41 11 16 78 c/o Ciba-Geigy Arg.

The XXI Annual Meeting of the International Society for Pediatric Neurosurgery will be held in Scottsdale, Arizona, 24–28 October 1993. *For further information, please contact:* Toby L. Anchie, Manager – BNI Administration, Barrow Neurological Institute, 350 West Thomas Road, Phoenix, AZ 85013, USA; (602) 285-3579 or 1-800-BARROW-1.

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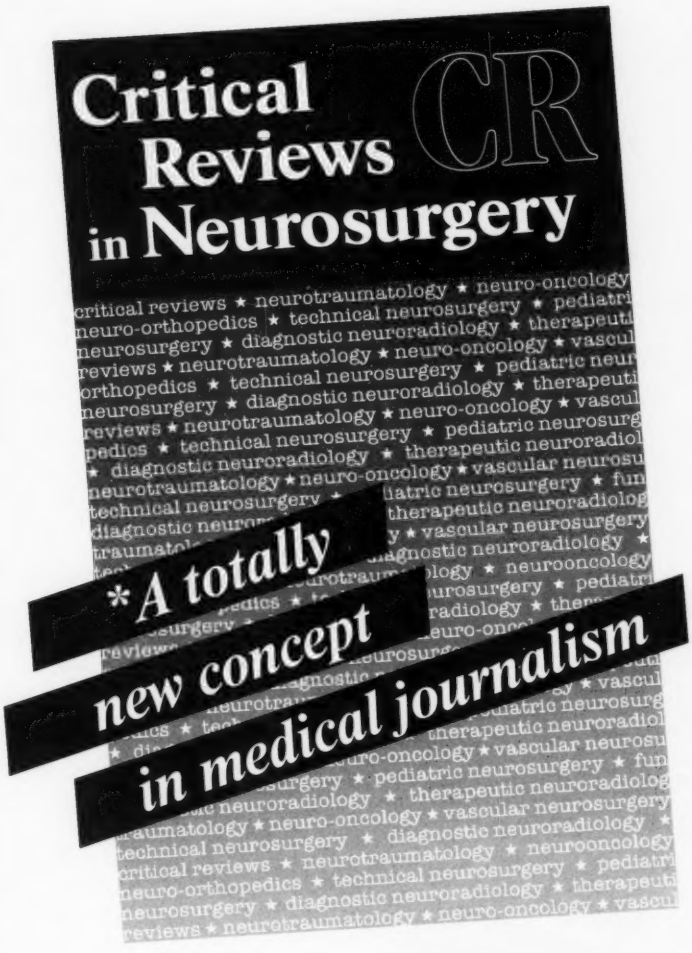

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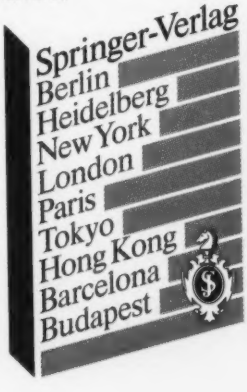

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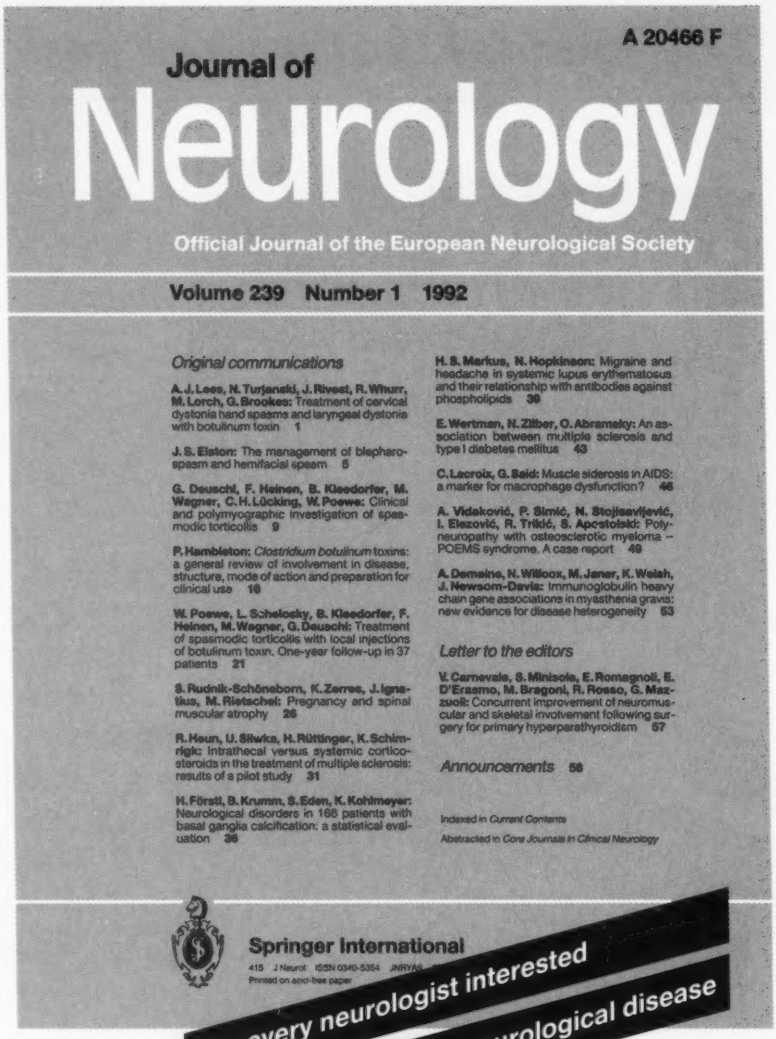
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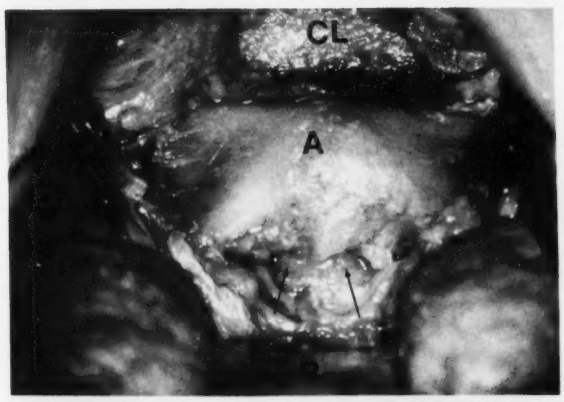

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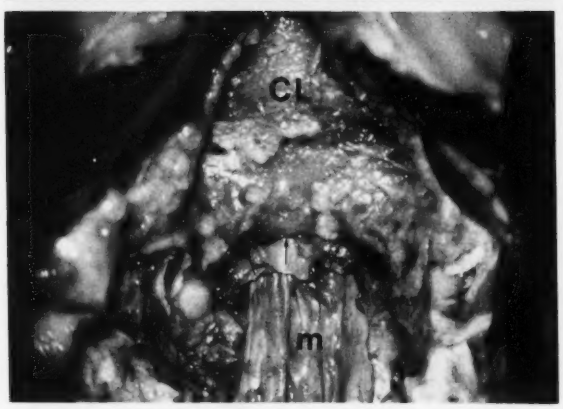

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Fig. 1.3. After the pharynx has been split along the median raphe and the rectus capitis anterior muscle has been dissected, the anterior arch of the atlas *(A)* is exposed. The tongue is depressed with a retractor *(R)*. *CL*, inferior margin of the clivus. The base of the ondontoid process is visible below the arch of the atlas

Fig. 1.4. The anterior rim of the arch of the atlas and the odontoid process have been resected. The caudal part of the cruciate ligament is exposed *(arrow)* as the transversal ligament is retracted with a dissector.

Fig. 1.5. After the soft palate has also been split, the lower half of the clivus may be exposed *(CL)*. *m* Tectorial membranes. The anterior margin of the foramen magnum is marked by *arrows*

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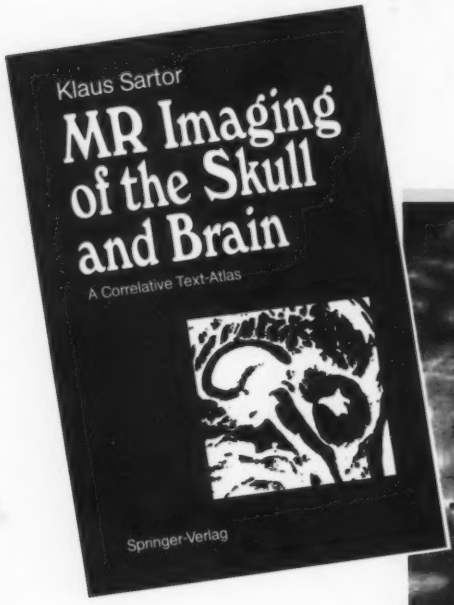

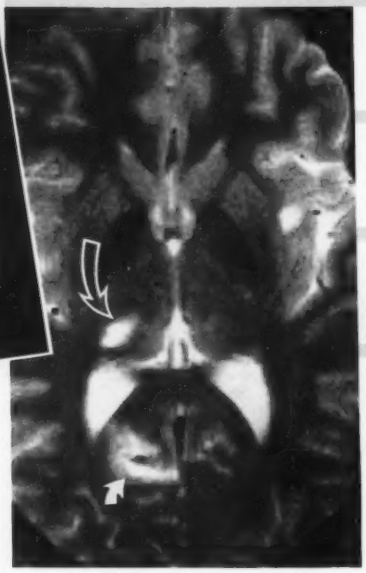

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